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NAME OF SUPERVISOR / NOM DU DIRECTEUR DE THÈSE Dr A.J. JONES

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CARBON-13 NMR: CONFORMATION ANALYSIS OF NITROGEN AND PHOSPHORUS HETEROCYCLES, AND DIENONES

by

© PETER HANISCH

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

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THE UNIVERSITY OF ALBERTA

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

CARBON-13 NMR: CONFORMATION ANALYSIS OF NITROGEN AND PHOSPHORUS HETEROCYCLES, AND DIENONES

submitted by PETER HANISCH

in partial fulfilment of the requirements for the degree of Master of Science in Chemistry.

.....
Chairman

.....

.....

Date. November 7th 1975.

DEDICATION

The Graduate Students and Postdoctoral Fellows of the Chemistry Department at the University of Alberta

ABSTRACT

This treatise describes a study of the conformation of nitrogen and phosphorus heterocyclic compounds using carbon-13 nuclear magnetic resonance methods. Isolation and assignment of the configuration of the three diasteroisomers of 1,3,5-trimethyl-4-phenylpiperidin-4-ol and the conformational effects in 2,2,6,6-tetramethyl substituted piperidine rings are described. In addition, the possibility of detecting boat (non-chair) conformations in 4-phenylpiperidin-4-ol derivatives is discussed. A carbon-13 nmr solvent study of the model system, 3-piperidinol, was carried out to detect conformations where intramolecular hydrogen bonding interactions of the type -N---H-O- are possible. Several 3-tropinone derivatives were studied and evidence is presented for boat (non-chair) conformations where similar -N---C=O and -N---H-O- interactions are implicated.

Several representative six-membered ring phosphorus heterocycles were also studied in both the PIII and PIV oxidation states. Evidence is presented for the predominance of axial phenyl groups in several 1-phenylphosphorinanes. Additivity effects were derived for the phosphorus systems and comparisons made with analogous nitrogen heterocyclic parameters. The effect of the PIV oxidation state upon the chemical shifts in the aromatic ring of various phenyl phosphine oxides and the consequent valence bond structure of these oxides is reported.

As a corollary, the chemical shifts of several dienones used as synthetic precursors in the above studies are reported and the effect of introducing a cross-conjugated double bond to the enone in acyclic and alicyclic systems is discussed.

ACKNOWLEDGEMENTS

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TABLE OF CONTENTS

Chapter		Page
ONE	INTRODUCTION	1
	A. Conformational Analysis of Non-Chair Structures - A Brief Review	1
	B. Carbon-13 Additivity Effects	7
	C. Carbon-13 nmr in Conformational Analysis	12
	D. Phosphorus Heterocycles	16
	E. Carbon-13 Chemical Shifts of Selected Dienones	19
	F. ^{13}C NMR: Principles of Data Acquisition	19
	Spectral Interpretation	21
	G. Experimental	22
TWO	NITROGEN HETEROCYCLES	24
	A. The Stereochemistry of 1,3,5-Trimethyl-4-piperidone and its 4-Phenylalcohol Derivatives	24
	Introduction	24
	Results	25
	Discussion	
	B. The Stereochemistry of 1,2,2,6,6-Pentamethyl-4-piperidone and Some of its Derivatives	35
	Introduction	35
	Results	38
	Discussion	46
	1. General Additivity Effects in the 2,2,6,6-tetramethyl System	46
	2. Specific Conformational Effects	47

TABLE OF CONTENTS (cont'd)

Chapter		Page
	a. 2,2,6,6-Tetramethylpiperidine Derivatives..	47
	b. 1,2,2,6,6-Pentamethylpiperidine and -4-Piperidinol.....	51
	c. 1,2,2,6,6-Pentamethyl-4-piperidone.....	53
	d. 1,2,2,6,6-Pentamethyl-4-phenyl-4-piperidinol	59
	i. Intra-molecular Hydrogen Bonding - A Model Study.....	59
	Conclusions.....	67
	Experimental.....	68
THREE	TROPANES.....	72
	A. Introduction.....	72
	B. Results.....	73
	C. Discussion.....	83
	1. Additivity Effects.....	83
	2. Tropane Conformations.....	84
	a. Protonation Effects.....	84
	i. Ecgonine Methyl Ester (45).....	87
	ii. 3α-Diphenylhydroxymethyl-3β-tropanol (49)	90
	iii. Ethyl 3α-phenyltropane-3β-carboxylate (47).....	90
	iv. 3α-Phenyltropane-3β-carboxylic acid (48)	92
	v. 3α-Phenyl-3β-tropanyl phenyl-ketone....	92
	D. Conclusions.....	95
	E. Experimental.....	96

TABLE OF CONTENTS (cont'd)

Chapter		Page
FOUR	PHOSPHORUS HETEROCYCLES	97
	A. Introduction	97
	B. Results	99
	C. Discussion	104
	1. Phosphorinane Derivatives	104
	a. 1-Phenylphosphorinane (51) and 1-Phenyl-4-phosphorinanone (15)	104
	b. 1-Phenyl-2,2,6,6-tetramethylphosphorinanes	105
	c. Conformational Analysis of 1-Phenyl-2,2,6,6-tetramethyl phosphorinanes	106
	d. ^1H Chemical Shift and J_{PH} Coupling	110
	e. ^{13}C Additivity Relationships	114
	f. 1-Phenyl-3,5-dimethyl-4-phosphorinanone (58)	114
	2. Phosphorinane Oxide Derivatives	118
	a. (i) Conformational and Additivity Effects.	118
	(ii) P-atom Hybridization	121
	b. The Phosphorus-Oxygen Bond	121
	3. Mono-, Di- and Triphenylphosphine and their Oxides	122
	4. The 8-Phosphabicyclo|3.2.1.|octan-3-one System.	126
	5. Phosphorus, Nitrogen and Carbon Comparisons	129
	D. Conclusions	132
	E. Experimental	134

TABLE OF CONTENTS (cont'd)

Chapter		Page
FIVE	DIENONES	138
	A. Introduction	138
	B. Results	140
	C. Discussion	140
	1. Olefinic and Carbonyl Carbons	140
	2. Methyl Carbons	145
	D. Conclusions	146
	E. Experimental	147
REFERENCES		149

LIST OF TABLES

Table		Page
I	Substitution Effects in Monosubstituted Cyclohexanes...	14
II	Carbon-13 Chemical Shifts of 1,3,5,-Trimethyl-4-piperidone, the α-, β- and γ-4-phenyl-4-ol Derivatives and their Corresponding Hydrochlorides.....	26
III	Proton Chemical Shifts and Coupling Constants of the N-Me and C-Me Protons in the α, β and γ Free Bases and Hydrochlorides.....	29
IV	The Carbon-13 Chemical Shifts of 1-, 1,3(ax)-, 1,3(eq)-, 1,3(eq),5(eq)- and 1,3(ax),5(ax)-Trimethyl-4-phenyl-piperidin-4-ols, their Hydrochlorides and the Derived Equatorial Methyl Additivity Parameters.....	32
V	Carbon-13 Chemical Shifts of 4-Methylene-, 4-oxo- and 4-ol Derivatives of NH and NCH_3 Piperidines.....	39
VI	Carbon-13 Shifts of 1-, 1,2,6(trans)- and 1,2,2,6,6-Methylated 4-phenylpiperidin-4-ols.....	40
VII	Protonation Effects on Carbon-13 Chemical Shifts of 1-, 1,2,6(trans)- and 1,2,2,6,6-Methylated 4-phenylpiperidin-4-ols in Certain Solvents.....	41
VIII	Additivity Parameters for Introduction of 2,2,6,6-Tetramethyl Substituents to some Piperidine Derivatives and 3,3,5,5-Tetramethyl Substituent to Cyclohexanone.....	43
IX	Solvent Study of 3-Hydroxypiperidine(20): CMR Shifts	44
X	Carbon-13 Chemical Shifts of $CHCl_3 \cdot HCl$ and $H_2O \cdot HCl$ in Various Solvents.....	45

LIST OF TABLES (cont'd)

Table		Page
XI	PMR Solvent Study of 1,2,2,6,6-Pentamethyl-4-phenyl-4-piperidinol	63
XII	The Carbon-13 Chemical Shifts of Tropane Derivatives	74
XIII	Additivity Effects of the Introduction of the C-6,7 Ethylene Bridge to the Piperidine Ring System	85
XIV	Protonation Effects on the Carbon-13 Chemical Shifts in Various Tropanes	86
XV	Carbon-13 Chemical Shifts in P-Phenyl-Phosphorinane and Phosphorinane Oxide Derivatives	100
XVI	^{13}C-^{31}P Nuclear Spin Coupling Constants for P-Phenyl-Phosphorinane and Phosphorinane Oxide Derivatives	101
XVII	P-Oxide Substitution Parameters for P-Phenyl-Phosphorinane Derivatives	102
XVIII	Empirical Tetramethyl Parameters Observed in P-Phenyl-Phosphorinane Derivatives	103
XIX	$^{3}J_{P-H}$ Coupling Constants, Proton Chemical Shift and Shift Differences for the Methyl Protons in 2,2,6,6-Tetramethylphosphorinane, Phosphine and Phosphine Oxide Derivatives	112
XX	Carbon-13 Chemical Shifts of 1-Phenyl-3,5-Dimethyl-4-Phosphorinanone Isomers and Major P-oxide Isomer	115
XXI	^{13}C Chemical Shift, J_{PC} Coupling Constants and Oxide Additivity Parameters in Mono-, Di- and Triphenyl-phosphine and their Oxides	124

LIST OF TABLES (cont'd)

Table		Page
XXII	^{13}C Chemical Shifts and J_{PC} Coupling Constants of 8-phosphabicyclo|3.2.1.|octan-3-one Derivatives.....	128
XXIII	Carbon-13 Chemical Shifts of Some Acyclic Enones and Dienones.....	141
XXIV	Carbon-13 Chemical Shifts of Alicyclic Enones, Dienones and Supporting Derivatives.....	142

LIST OF FIGURES

Figure		Page
1.	β-chair and β-boat forms of 2-bromolanost-8-ene-3-one (1).....	3
2.	The γ-Effect: γ-gauche a or eclipsed arrangement produces an upfield shift of the carbon signal relative to the shielding of the corresponding carbon in the anti form b.....	10
3.	The δ-Effect: The relative orientations of the δ-groups C and X.....	11
4.	Δqc_γ Varying with Dihedral Angle (Θ).....	52
5.	Pmr Spectrum of the $CHCl_3 \cdot HCl$ extract in (a) $CDCl_3$, (b) D_2O, and (c) $CDCl_3$ after being in contact with D_2O.....	55
6.	Interaction between water of hydration and nitrogen....	57
7.	Proton exchange between $\overset{\oplus}{N}$-H and solvent (H_2O).....	60
8.	Representation of intra-molecular hydrogen bonding in a non-polar solvent (a) and solvation (b) in a polar solvent (S).....	65
9.	Suggested conformational aspects on protonation of a tropane molecule existing in a preferred boat conformation in a (free base) and c (hydrochloride) due to the intra-molecular hydrogen bonding nature of the hydroxyl group	88
10.	Lithium Aluminum Hydride reduction of 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanone.....	109

LIST OF FIGURES (cont'd)

Figure		Page
11.	A Karplus relationship between the $^{2}J_{PH}$ coupling constant and dihedral angle (θ) (——)[63b] and the $^{2}J_{PC}$ coupling constant and dihedral angle (— , - - -).....	111
12.	Carbon-13 chemical shifts for C-2,6, C-3,5 and C-4 carbon positions in analogous C, N and P six-membered rings.....	131

CHAPTER ONE

INTRODUCTION

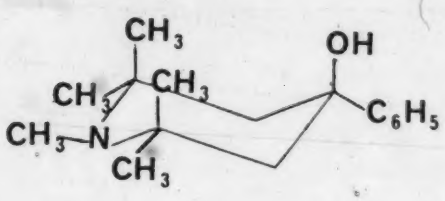
A. Conformational Analysis of Non-Chair Structures - A Brief Review

Conformational analysis had its origins around the late 19th century when Sachse[1] suggested that cyclohexane could adopt two possible arrangements, later termed the 'chair' and 'boat' conformations. It is now well established that cyclohexane exists predominantly in the chair form, which is thermodynamically more stable than the boat. The boat conformer is destabilized by the presence of two eclipsed ethane type interactions and non-bonded interactions between the two 'flagpole' hydrogen atoms. Further, Hazebroek and Oosterhoff[2] have provided evidence, from a statistical mechanical study, that while the chair is rigid and unable to have any relative motion of the ring carbons without distortion of bond angles, the boat form has a considerable amount of such motion possible. This pseudorotation transforms the classical boat into a preferred twist or flexible form. Unequivocal choice between the two conformations is not possible due to the high mobility of such forms.

The question of non-chair structures contributing to the conformation of a variety of systems has subsequently been widely discussed[3-24]. It is informative to consider these contributions in their chronological order. Thus in 1951, Johnson[3] suggested that intramolecular interactions in several polycyclic molecules containing six-membered rings induce a preference for the boat conformation. However, it was not until 1957 that this feature was demonstrated by

Barton and co-workers[4]. Two monobromo derivatives of lanost-8-en-3-one were obtained and their structures verified by chemical means. Both had identical IR and UV absorption spectra characterizing an equatorial bromine substituent. Since it is impossible to have a pair of isomers for 2-bromolanost-8-en-3-one (1) having an equatorial bromine in a chair conformation it was concluded that ring A in the 2β-bromo-ketone should be in a boat form (Figure 1). The 1,3-diaxial interactions between the bromine atom and two methyl groups at C-4 and C-10 in the β-chair form can be relieved upon transforming to the boat conformer. Final verification was obtained in a pmr study by Abraham[5]. Since that time many other occurrences of boat conformations in steroidal systems have been reported[6-9].

A study by Lyle[10] on the properties of 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (2) revealed that acetylation was restricted compared with 1-methyl-4-phenyl-4-piperidinol. Further, the infrared absorabsorption spectrum of the 1,2,2,6,6-pentamethyl system indicated intramolecular hydrogen bonding. The explanation offered considered the severe non-bonded interactions of the three axial groups in 2a compared with the stabilizing influence of hydrogen bonding in 2b thus favoring the boat conformation 2b.



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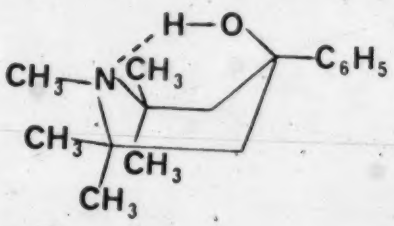

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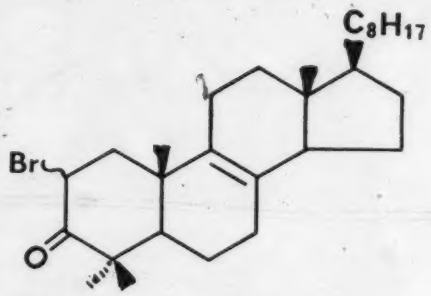

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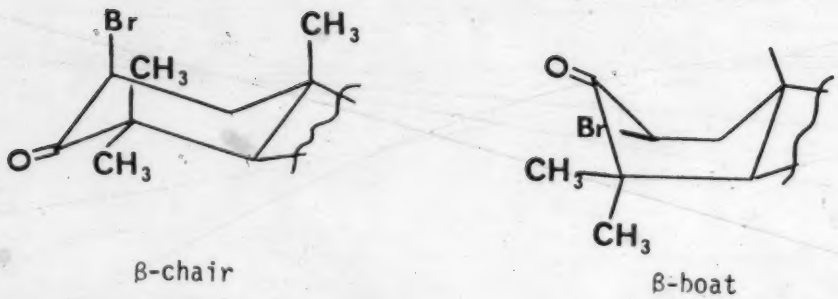
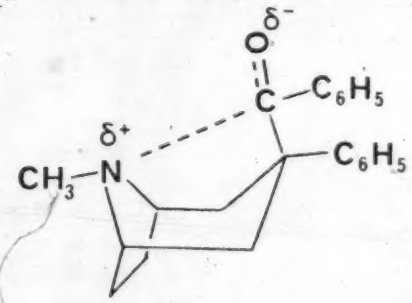


β-chair β-boat

FIGURE 1: β-chair and β-boat forms of 2-bromolanost-8-en-3-one (1).

Other examples of this additional stabilization in the boat conformation are 3α-phenyl-3β-tropanyl ketone (3)[11], r-2-cis-5-di-t-butyl-cis-1,4-dihydroxycyclohexane[12] (4) and the A ring of 2β-amino-5-α-cholestan-3-α-ol (5)[13].



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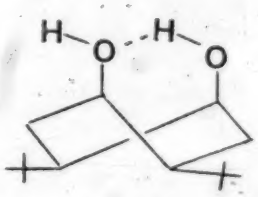

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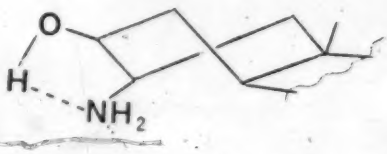

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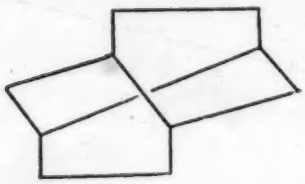
A variety of attempts to classify molecules according to the factors which contribute to favouring non-chair conformations have been put forward. According to Kumler and Huitric[14] the six-membered ring system most likely to prefer boat conformations must meet two restrictions. 1) The ring possesses two or more atoms that are not sp^3 hybridized. 2) One atom in the ring is not sp^3 hybridized, and a strong dipole exists on the adjacent atom. The first case is exemplified by 1,4-cyclohexadiene, while an historically important though incorrect example[15] of the latter are the α-halocyclohexanones.

According to a recent review by Kellie and Riddell[16] non-chair conformations can be classified as follows:

1) Molecules constrained into non-chair forms by chemical bonding.
2) Molecules with an inherent preference for non-chair forms.

3) Molecules forced into non-chair forms by the magnitude of strain present in their chair conformations.

The first class contains such molecules as twistane (6) and bicyclo[2.2.2.]octane (7). These having a bridge constraining the structures into non-chair forms



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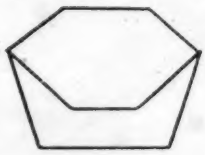

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The second class corresponds to the proposition of Kumlar and Huitric[14], examples being 1,4-cyclohexadiene and the analogous dioximes. 1,4-Dimethylenecyclohexane[17] and its exo-tetramethyl analogs are also suggested to exist in a non-chair conformation, but X-ray studies[18] of the exotetracyano derivative indicate the chair form to be the most stable.

The third class represents the majority of non-chair conformations. A shift in conformational equilibrium from chair to boat could be more effective if unfavourable interactions present in the chair form are relieved during the interconversion. This is best exemplified by the trans-1,3 and cis-1,4-di-t-butylcyclohexanes. The severe non-bonded interactions of the t-butyl groups are removed upon conversion to the

twist conformer. In some molecules, not only are the interactions in the chair form eliminated but also stabilizing interactions such as intramolecular hydrogen bonding in the boat form, cause the latter conformer to be preferred as in 2b, 3, 4 and 5.

The majority of common physical methods have been applied to study contributions made by non-chair conformations. These include X-ray[19], ORD-CD[20], IR and UV absorption spectroscopy[21]. dipole moments[22] and proton magnetic spectroscopy[23,24]. In the light of the success of the pmr investigations we elected to test the validity of using ^{13}C magnetic resonance techniques in this area since it is clear that carbon-13 chemical shifts strongly reflect steric influences particularly important in the relief of syn-axial interactions in chair conformations and the introduction of flagpole interactions in boat forms.

In order to compliment the ^{13}C study on the -N---H-O- and -N---C=O intramolecular hydrogen bonding type interactions as present in compounds 2 and 3 we used 3-hydroxypiperidinol as a model system. The -N---HO-interaction in this molecule is established[25]. A solvent study on the configurational equilibrium of this molecule using cmr can be discussed in relationship to the potential effects of hydrogen bonding on the chemical shifts of the piperidine ring carbons.

During the course of these investigations some approaches to the use of cmr to study non-chair structures have been reported[26a,26b]. In these examples, it is apparent that breakdown in accepted substituent additivity parameters provide the principal mechanism for describing conformational contributions from non-chair structures. We elaborate this feature in the following section.

B. Carbon-13 Additivity Effects

An important aspect for the application of ^{13}C data to structural and conformational elucidations, is the use of simple additivity relationships, correlating the shieldings within a closely related series of compounds with a number of structural parameters. This correlation was first noted by Lauterbur[27] and his proposal extended by Savitsky and Namikawa[28] and later in a most detailed study by Grant and co-workers[29,30].

For linear hydrocarbons five parameters are necessary to define the shieldings. These are defined as α, β, γ, δ and ε, i.e. the shifts produced along the chain on that particular labelled carbon position on replacing a hydrogen atom with a substituent group. All of these parameters, with the exception of the γ-effect are paramagnetic, the gamma-gauche effect being diamagnetic. For example, in the alkanes the α-effect C-H → C-X causes a deshielding of ≈9 ppm, the magnitude varying between various families of compounds. The β-effect C-CH C-CX is similar in magnitude to the α-effect. The γ-effect is a shielding effect (2.5 ppm) C-CCH → C-CCX. This effect has important implications for stereochemical studies (vide infra). The δ and ε effects are quite small, +0.3 and +0.1 ppm, respectively, in this series.

The α-effect can be explained by charge polarization effects[31]. Removal of electronic charge from the carbon by substituting a proton for a methyl group creates a small increase in effective nuclear charge of the remaining orbitals. Thus decreasing the average orbital radius causing the $\langle r^{-3} \rangle_{2p}$ term of the Karplus-Pople equation[32] to be enlarged, hence a downfield shift.

$$\sigma_p = -\frac{e^2h^2}{2m^2c^2\Delta E} \langle r^{-3} \rangle_{2p} \sum_B Q_{AB}$$

Cheney estimated[31] the change in the paramagnetic shielding constant, σ_p, to be less than 2 ppm for a molecule containing a β-methyl group and 0.5 ppm for a γ-methyl group. Hence it was suggested, that since the inductive effect does not significantly deshield the carbon position other than at the α-position, that this does not serve as an explanation for the β- and γ-methyl substituent parameters. The latter were thought to be steric in origin. The steric interaction with the β-methyl causes a contraction of the orbitals of the atom of interest, hence resulting in a downfield shift. The γ-effect, exemplified by methylcyclohexane, follows from the possible steric polarization of electrons along the C-H bond at the γ-position due to non-bonded interactions across the ring such that the carbon nucleus is shielded and the attached protons are deshielded.

Further discussion of the γ- and δ-effects is warranted since they are both used extensively in this research.

The γ-1,4 gauche-effect was recently reviewed by Pehk and Lippmaa[33] and Eliel and co-workers[34]. This diamagnetic effect was first mentioned by Grant and Paul in the alkane series[30a,35], later for cyclohexane derivatives[36] and subsequently proposed[36] as a method for conformational analysis of such compounds but without any theoretical interpretation.

The γ-effect shows some regularities. It is diamagnetic and increases with decreasing interatomic distance between the 1 and 4 atoms

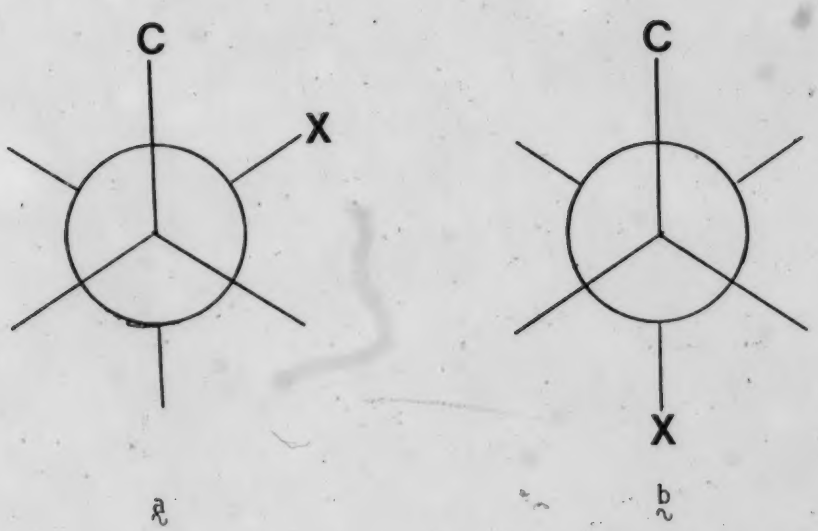
(Figure 2) but the number of interacting heavier atoms and not just the distance between them is important since the δ-effect is usually deshielding even with short H---H interactions[37].

The 1,4-interaction is not additive, in fact it is different for different nuclei, appearing also in spectra of ^{15}N, ^{17}O, ^{19}F and ^{31}P [38] and can even be unequal for the nuclei of the same type in different positions in the molecule.

An important contribution to the studies on the γ-effect was presented by Eliel and co-workers[34]. They observed that, while 2nd row heteroatoms (N, O, F) cause significant upfield shifts in the resonance of anti-periplanar carbon nuclei, a methyl or methylene group or 3rd row heteroatoms (S, Cl) demonstrate negligible (<1 ppm) anti effects. In fact a gauche heteroatom (Figure 2a) results in an upfield shift of the carbon-13 signal greater than the upfield shift caused by a methyl or methylene group. These authors proposed[34] the following mechanism to explain the unique role which N, O, and F play in the γ-anti shift. "Partial π-bond involvement of the free-electron pairs of these second-row elements is favoured by the shorter C-X bond and the more nearly similar radial dimensions of these atoms with that of carbon. Conversely Cl and S have larger covalent radii and less favourable radial matching with the pπ - orbitals of carbon."

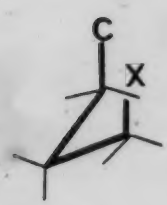
The deshielding δ-1,5 interaction effect was first noted by Roberts[39] and its stereochemical dependence was later discussed by Stothers[37]. The δ-groups may have various orientations as shown in Figure 3.

The δ-effect is largest and most distinctive for molecules with the syn-axial orientations, generally being of the order of 2-3 ppm

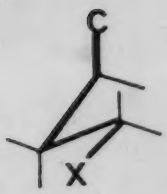


a b

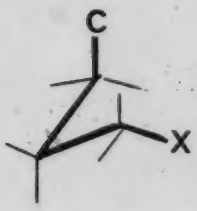
FIGURE 2: The γ-Effect: γ-gauche a or eclipsed arrangement produces an upfield shift of the carbon signal relative to the shielding of the corresponding carbon in the anti form b.



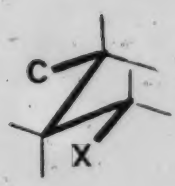
Syn-axial



Gauche-trans



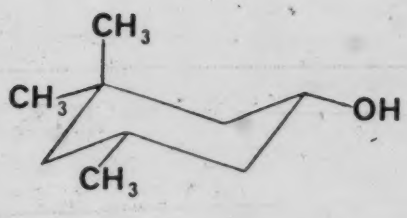
Gauche-gauche



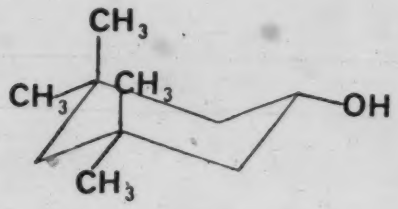
Trans-trans

FIGURE 3: The δ-Effect: The relative orientations of the δ-groups C and X.

for non-rigid molecules[37] and as high as 6.6 ppm in rigid molecules[37]. The former can be exemplified by comparing structures 8 and 9.



8



9

The introduction of the extra methyl causes the C3' axial carbon in 8 to be deshielded by 2.1 ppm. In a rigid system the deshielding is more enhanced, the introduction of a methyl at the C-8 position in 1-methylnaphthalene causes the 1-methyl carbon to be deshielded by 6.6 ppm.

The gauche-trans and gauche-gauche δ-effects are small, in the reported cases <1 ppm. In fact, for two methylnorbornane derivatives a small shielding effect was observed. The trans-trans δ-effect shown by exo-6-methyl-exo-2-norbornanol exhibits a 0.9 ppm shielding effect.

The deshielding effect appears to be more pronounced when there exists steric crowding of the δ-groups, hence differing from the behaviour found for the γ-nuclei.

C. Carbon-13 nmr in Conformational Analysis

Dalling and Grant[30b,40] have characterized the effect of

methyl substitution in a series of methylated cyclohexanes and aided by additivity parameters, obtained from the unequivocal assigned chemical shifts of certain derivatives, were able to assign the entire series with little ambiguity. At room temperature only average ^{13}C chemical shifts are obtained while lowering of the probe temperature enables isolation of the individual spectra of the axial and equatorial conformers. The axial methyl carbon resonates 6 ppm to high field of the equatorial one. Further comparisons can be made by observing the shieldings for cis- and trans-4-t-butylcyclohexyl derivatives[40,41]. In general the equatorial substituent deshields the α, β and γ carbons relative to the effect of an axial group. As can be seen from the Karplus-Pople equation mentioned earlier the paramagnetic shielding parameter is directly dependent on the charge density, hence the chemical shift of the cyclohexane ring will depend on the substituent's electronegativity. Table I lists representative data for various cyclohexane substituents.

The carbon chemical shifts and conformational analysis of various nitrogen heterocycles has been described by several authors[34,43-47] and particular interest in those related to analgesic activity have been studied in our laboratory.

A particular area where pmr has proved to be useful has been in studies related to the nature of stereo-structural activity relationships in analgesically active components including derivatives of 4-phenylpiperidines[48] and 6,7-benzomorphans[49]. It has been established[50,51] that the analgesic potency of morphine and synthetic analgesics correlate with the attainment of a configuration in which the phenyl group is axially orientated. Casy and co-workers utilizing pmr identified the axial phenyl conformation in certain 4-phenylpiperi-

TABLE I

Substitution Effects[a] In Monosubstituted Cyclohexanes[42]

Substituent	α	β	γ	δ	% Axial
CH_3	5.8	8.4	-0.5	-0.6	5
COOH	16.1	2.0	-1.4	-1.0	9
COOMe	15.8	2.0	-1.6	-1.2	10
NH_2	23.5	10.1	-1.8	-1.1	12
OH	42.4	8.4	-2.6	-1.2	25
Cl	32.2	9.6	-2.4	-2.0	35
Br	25.0	10.3	-1.5	-2.0	35
I	4.2	12.2	-0.2	-2.1	33

[a] In ppm. Negative and positive values indicate upfield and downfield shifts, respectively.

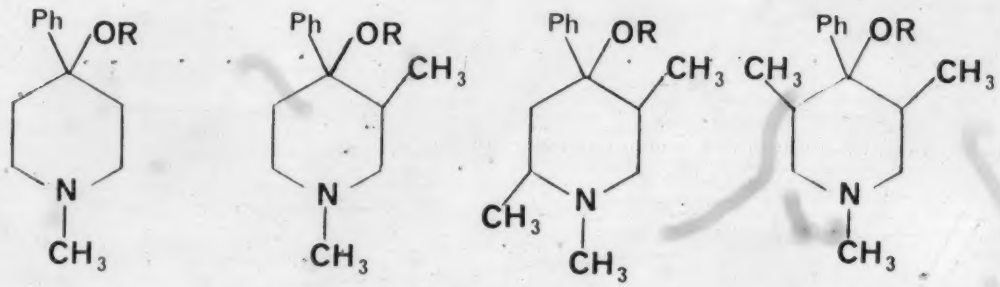
dines[48,52] (i.e. promedol) and 3α-phenyltropane-3-β-carboxylate hydrochloride[24]. The latter, being the tropane analog of pethidine is more active an analgesic than its parent[24] and furthered the axial phenyl hypothesis for analgesic potency. In the latter study[24] a variety of similar tropane derivatives were described which were postulated to possess the -N---H-O- type intermolecular interactions discussed earlier. Hence we chose to use ^{13}C magnetic resonance methods in these systems to determine the value of ^{13}C nmr as a tool for conformational analysis of systems in which non-chair contributions were likely to be dominant, in particular, those systems involving intramolecular interactions.

Further it should be mentioned that the non-chair conformation is a feature of particular importance in various pharmacological active molecules. Casy has proposed non-chair conformations for the active benzomorphan isomers[49] and the activity of certain ganglionic and neuromuscular blocking agents have been ascribed[53] to the steric crowding leading to chair deformations.

As a continuation of previous work in our laboratory on the potential of the ^{13}C magnetic resonance techniques as a tool in the determination of stereochemistry in analgesics[43,54,55,56] the conformation of the three diasteroisomers of 1,3,5-trimethyl-4-phenyl-4-piperidinols (13) have been determined in this study.

The 1,3-dimethyl-4-phenyl-4-piperidinols (11a) (the prodinols) and their corresponding propionate esters 11b (the prodines) have been investigated[55] along with the narcotic analgesic trimerperidine 12b, promedol, its isomers[56] and their precursors, 1,2,5-trimethyl-4-phenyl-4-piperidinols[56] 12a and the non-methylated 1-methyl-4-phenyl-4-

piperidinol derivatives[55] 10a, 10b..



10 11 12 13

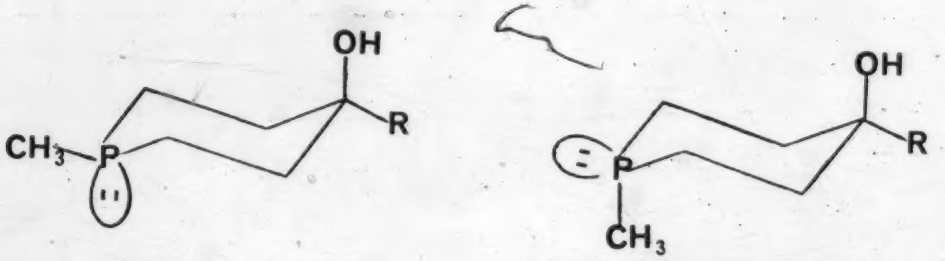
a) R = H b) R = CO Et

The establishment of the stereochemistry in all of the compounds 10, 11 and 12 was aided by use of empirical substituent parameters from carbon-13 studies of a series of substituted 4-piperidines[43] and 4-phenylpiperidines[46] of pharmacological interest. In particular, the clarification of the conflicting evidence[52,57-59] of the stereochemistry of the three isomers, α, β and γ of 12b involved the reversal of the prior assignment of the β and α isomers and hence prompted the study of the α, β and γ isomers of 13a.

D. Phosphorus Heterocycles

In contrast to the numerous studies available concerning the conformation of six-membered ring heterocyclic compounds containing O, N or S very little attention has been paid to the corresponding tervalent phosphorus system. Only in the past few years have workers turned to this challenging problem[60-81].

The configurational stability for tervalent phosphorus, having a high barrier to inversion, has been demonstrated by Quin and co-workers[60,61] in isolating the cis- and trans-isomers of various phosphorus heterocycles. It is therefore interesting to compare the conformational stabilizing influence of phosphorus compared with the freely inverting nitrogen atom in analogous compounds. Thus, in the 1-methyl-4-alkyl-4-phosphorinanols 14[60,61] a configurational difference was observed at the phosphorus atom for the two isomers while in the corresponding nitrogen system only one diasterisomer is observable.



14-cis 14-trans

Little preference for either equatorial or axial configuration of the P-CH_3 group is evident. (cis:trans >0:30).

Predominance of an axial phenyl group at the phosphorus atom in 1-phenyl-4-phosphorinanone 15 and its dimethyl ketal 16 is shown in the solid state by X-ray analysis[62]. Earlier Albrand et al.[63a] developed a relationship between $^2J_{PCH}$ and the dihedral angle α and assigned the solution conformation of 15 as a chair or possibly a boat, with the phenyl group equatorial. However, taking into consideration the X-ray data Quin suggests[62] that Albrand's calculations may be in error.

Recently the axial preference for phosphorus substituents in

six-membered rings has been reported for alkyl (except t-butyl) and aryl groups in 2-phospha-1,3-dioxa-[64] and 2-phospha-1,3-dithiacyclohexanes[65] and for various substituents (Z = Cl, OCH_3, CH_3, iPr and Ph) in 5-t-butyl-2(Z)-1,3,2-dioxaphosphorinanes[66,67] in predominantly chair conformations. Further, Lambert et al.[68] have shown that the proton on phosphorinane prefers the axial orientation. The axial preference in these systems has been attributed to favourable P and O lone-pair interactions[67] influencing the torsional barrier of the phosphorus or the possibility that the syn-axial interactions may be greatly reduced[66] since the phosphorus-oxygen bonds are considerably longer than the carbon-oxygen bonds and because of possible consequent flattening of the ring about phosphorus.

There are distortions from cyclohexane geometry in the phosphorinane compounds, the P-C bond being 0.33Å longer than the C-C bond, the <CPC bond angle used for discussions taken as 100° [69]. The widening of the ring around phosphorus increases the puckering at C-4, the axial substituent at this position being projected slightly towards the ring. Hence conversion of a chair form, with an equatorial P-substituent into its boat conformer causes severe flagpole-bowsprit interactions, this not being the case with an axial P-substituent.

High resolution ^1H and ^{31}P nmr have been employed[70a-d] for structural determination of organophosphorus compounds. However, in most cases the ^{31}P spectra give rise to only one chemical shift parameter. This, together with the fact that the proton signals occur in a very narrow range and are thus difficult to assign suggests that ^{13}C nmr studies would be valuable.

During the course of this work several reports have appeared

concerning J_{CP}[71-77] coupling constants obtained from direct measurement of the ^{13}C nmr spectra of selected alicyclic[71,72], acyclic[73,74] and heteroaromatic[75,76,77] phosphorus derivatives. Evidence has been presented[74,78-81] that clearly shows a dependence of both $J_{^{13}C-^{31}P}$ coupling constants and ^{13}C chemical shift on structures in these compounds and thus our overlapping efforts have been supplemented by these results. Our efforts have been particularly related to the synthesis of phosphorus analogs of the nitrogen heterocycles described earlier. However, due to problems of compound stability only the phenyl analogs in the phosphorinanone compounds and derivatives were studied in detail. Supplementary data on the cyclic phosphines and their corresponding oxides are described. Some insight into the π-bonding in the P-O bond has been gained (compare ref. 82).

E. Carbon-13 Chemical Shifts of Selected Dienones

The nitrogen and phosphorus heterocyclic compounds described in this work were synthesized by amine or phosphine:dienone condensation. Since there is a paucity of data concerning the carbon chemical shifts of cross-conjugated ketones, phorone and pipertenone being the only examples[23], we elected to determine the ^{13}C-chemical shifts of the dienones. These results are described in Chapter V.

F. ^{13}C NMR: Principles of Data Acquisition

Proton magnetic resonance has grown into one of the most important methods of instrumental analysis routinely used by organic chemists. Nevertheless it is limited for two reasons.. First, the physical properties and reactivity of organic compounds are more

effectively explained by the carbon atoms and their bonding states than the protons. Secondly, many organic molecules give rise to extremely complex proton spectra covering a small range (≈10 ppm). The ^{13}C nuclei on the other hand absorb over a wide range of approximately 220 ppm and the ^{13}C spectra, routinely recorded with complete proton decoupling (vide infra) consist of single resonances (providing other magnetic nuclei are absent) for each individual carbon atom in the molecule.

The application of nmr to the ^{13}C isotope has two drawbacks. 1) Its low natural abundance (1.1%) and, 2) its low sensitivity, 1.6% compared to 'H resonances (100%) at the same magnetic field strength. The techniques for overcoming these difficulties have been reviewed in detail by Levy[84], Stothers[85] and Breitmaier[86]. We therefore describe the technique relevant to this present work, pulsed Fourier Transform NMR (PFT).

PFT nmr differs from the conventional steady-state experiment (continuous wave CW) in that the sample is irradiated with the pulse exciting all nuclei simultaneously away from their equilibrium orientation with the magnetic field, so generating a signal that, after the pulse, decays through relaxation processes (T_1, T_2) to zero and equilibrium is re-established. This free induction decay (FID) is the Fourier Transform of the steady state resonance[87].

Each FID is stored and accumulated in the computor memory and the spectrum is extracted by taking the inverse F.T. since the original signal, a modulated exponential decay, contains all of the information in the normal absorption pattern. Time averaging a series of FID signals provides a S/N ratio (signal to noise) enhancement of $\sqrt{n}$ with the added feature that the repetition rates can be much higher

than in the steady state operation. This leads to an additional improvement of up to 100 fold for a comparable sample time. One of the limiting factors in the experiment is the relaxation time of the resonance signals. The pulse repetition rate must be longer than the T_1 (spin-lattice relaxation time) for the resonances so that equilibrium can be re-established between successive pulses. In the PFT ^{13}C nmr experiment a heteronuclear lock signal, usually the ^{19}F signal of hexafluorobenzene or the ^{2}H signal of a deuterated solvent $CDCl_3$, C_6D_6, etc. is used to stabilize the field.

:Spectral Interpretation

'Off-resonance' proton decoupling is a technique which is a routine experiment to determine the kind of carbon substituents. The method involves placing an attenuated decoupling frequency outside the range of the Larmour frequencies of the protons, approximately 500 Hz from the optimal decoupling value. Hence, vicinal and long range couplings collapse and the characteristic first order splitting patterns for CH_3, CH_2, CH and quaternary carbons; quartet, triplet, doublet and singlet respectively, are readily discernible with residual couplings, J_r. The off-resonance spectrum suffers only a small decrease in S/N. In practice, quaternary carbons are detected since their signals are not affected by the decoupling frequency. Methyl and methine carbons are identified by the absence of a signal at the same position in both the decoupling and off-resonance spectra while a methylene carbon gives rise to a triplet centered at the position of the peak in the decoupled spectrum.

As a consequence of carbon-13 relaxation being dominated by proton-carbon dipole-dipole coupling, a carbon atom not directly bonded

to a proton is expected to give rise to a spectral line of lower intensity than the maximum possible from dipole-dipole relaxation (Nuclear Overhauser effect). Hence, this can be indicative of quaternary resonances present in the spectrum. Further proof of these resonance assignments can be obtained by a modulated off-resonance experiment in which the irradiation frequency is offset as before but the signal is modulated, thus effectively irradiating weak and small couplings, the quaternary resonances being 'decoupled' appear as sharp singlets.

A great asset of the spin decoupling technique arises from knowledge of the fully analyzed proton spectrum. That is, the carbon-13 spectrum may be assigned by directly relating each carbon resonance with an assigned proton resonance position by selective decoupling[88]. The experiment consists of aligning the decoupling frequency at the center of the multiplet of the protons directly bonded to the carbon atom to be assigned. Given a sufficiently spread out proton spectrum only the resonance due to the directly bonded carbon atom will be decoupled giving a single resonance whereas the other carbon atoms will remain coupled.

All of these techniques have been employed in the present work in order to establish spectral assignments.

G. Experimental

Carbon-13 nmr spectra were determined using a Bruker HFX-90 spectrometer operating at 22.63 MHz in conjunction with a Nicolet-1085, 20K memory, computer. The instrument consists of a deuterium lock system, a BSV-2 random noise (800 Hz band-width) proton decoupler and a BSV-2 pulse generator-amplifier. All samples were contained in

precision ground 10 mm, o.d., tubes. The spectrometer was used in the crosscoil configuration. On the average a 8 μs pulse, corresponding to an approximate tilt angle of 45°, was employed. The delay between pulses was 0.8 sec. for the average spectral width of 5000 Hz. Accumulation time averaged 30 mins. over 8K data points for concentrations of the order of 0.27 M. For off-resonance on coupled spectra this time was doubled. All carbon chemical shifts reported in this work are given in parts per million downfield from TMS. Hence a negative chemical shift parameter refers to an upfield shift, and a positive value, a downfield shift.

The pmr spectra were recorded using Varian Associates 60 or HA-100 spectrometers.

The experimental procedures for obtaining the compounds used in this work are reported at the end of the relevant chapter.

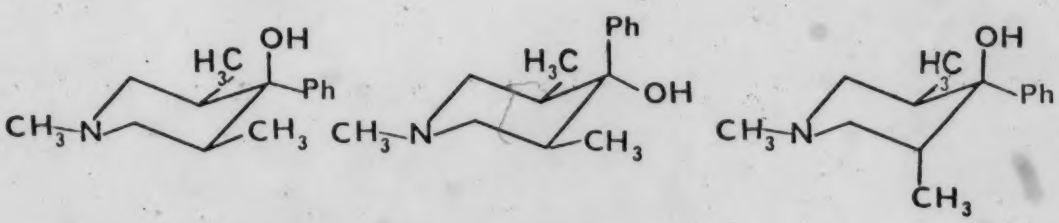
CHAPTER TWO

NITROGEN HETEROCYCLES

A. The Sterochemistry of 1,3,5-Trimethyl-4-piperidone and its 4-Phenylalcohol Derivatives

INTRODUCTION

The isolation of the three isomeric 1,3,5-trimethyl-4-phenyl-4-piperidinols from a phenyllithium reaction on the corresponding ketone has been described by Sorokin[89]. The structures of the three isomers were assigned as α, β and γ on the basis of the ease of esterification. No spectral evidence was reported.



α β γ

Sorokin also showed that the propionic ester hydrochlorides of the α- and β-isomers (cis Me-Me) were analgesically inactive, while the ester hydrochlorides of the γ-isomer (trans Me-Me) was as potent as promedol (See Chapter One). It was suggested that the inactivity of the cis-isomers may be due to the equatorial methyl groups hindering the formation of a drug-receptor complex. The inverted chair form of the γ-isomer

in which the phenyl group is axially orientated occurs only to the extent of 15%[90]. The active conformer therefore, has an equatorial phenyl group consequently defying the "axial-phenyl configuration requirement" described in Chapter One.

Since carbon-13 nmr studies[56] carried out in this laboratory had shown that the conformations of the four diastereoisomers in the analogous 1,2,5-trimethyl (promedol) derivatives were previously assigned incorrectly, it seemed desirable to repeat Sorokin's synthesis and to determine the conformation of the α, β and γ-1,3,5-isomers unequivocally using ^{13}C nmr methods.

RESULTS

The conventional labelling system for the piperidine ring is employed throughout this work. Carbon atoms in substituents are identified by a prime symbol for the number appropriate to the position of substitution on the piperidine ring. Phenyl ring carbons are labelled C-q, C-o, C-m and C-p.

The carbon-13 chemical shifts of 1,3,5-trimethyl-4-piperidone 17, its 4-phenylalcohol, α, β and γ-isomers and their hydrochlorides are given in Table II.

In the above compounds symmetry exists in all but the γ-isomer, in which the methyl groups are axial and equatorial at C-3 and C-5, respectively. In the α- and β-isomers the double intensity of the resonances due to the equivalent carbons C-2,6, C-3,5 and C-3',5' enable their distinction compared to the single intensity of the resonances due to C-1' and C-4. Typical low field shifts for a carbonyl resonance (∿200 ppm) distinguish the C-4 carbonyl carbonyl, while in the phenylalcohol isomers the C-4 resonance was identified using modulated

TABLE II

Carbon-13 Chemical Shifts[a] of 1,3,5-Trimethyl-4-piperidone, the α-, β- and γ-4-phenyl-4-ol Derivatives and their Corresponding Hydrochlorides

Compound	Carbon Position											
	C-2	C-3	C-4	C-5	C-6	C-1'	C-3'	C-5'	C-q	C-o	C-m	C-p
17	64.3_5	43.6_9	210.6_6	43.6_9	64.3_5	45.0_4	11.4_3	11.4_3				
17a	60.4_2	41.0_5	205.2_1	41.0_5	60.4_2	43.2_6	10.9_5	10.9_5				
c 17a*	59.5_1[b] (57.5_2)	41.0_5 (39.2_8)	209.2_1 (93.0_1)	41.0_5 (39.2_8)	59.5_1 (57.5_2)	43.3_3	10.3_2 (9.5_0)	10.3_2 (9.5_0)				
α	58.9_1	40.8_3	75.9_6	40.8_3	58.9_1	46.1_2	12.2_4	12.2_4	145.6_0	128.0_7	126.3_4	125.1_6
α·HCl	55.8_3	38.7_9	74.6_1	38.7_9	55.8_3	43.4_3	11.9_8	11.9_8	142.9_6	128.2_3	126.9_4	124.5_8
β	60.2_6	43.9_7	76.6_6	43.9_7	60.2_6	45.6_9	13.2_7	13.2_7	141.5_6	127.7_4	127.3_1	126.5_0
β·HCl	57.9_4	41.2_1	74.5_0	41.2_1	57.9_4	43.6_4	12.5_2	12.5_2	139.2_4	129.4_2	128.2_3	127.2_6
γ	58.4_8	42.1_9	76.2_8	31.5_0	59.4_5	46.5_6	16.6_2	12.8_4	145.4_9	128.0_2	126.7_7	126.3_4
γ·HCl	56.2_1	41.0_5	74.9_7	30.1_6	56.2_1	44.5_6	15.9_7	12.5_9	143.0_6	128.2_8	126.4_5	127.4_7

[a] Given in ppm downfield from TMS. Solvent: $CDCl_3$ except * D_2O.

[b] Values in parenthesis are approximately 10% the intensity of the parent resonance.

[c] Original data converted using $\delta_c^{Dioxane} = 66.7_4$ ppm.

off-resonance methods. An off-resonance decoupled spectrum exhibited a characteristic triplet pattern about the lower field resonance and a doublet for the methine carbon resonance (40-43 ppm). Quartets about the highest field resonances (10-13 ppm) defined the C-3',5' methyl carbon atoms.

For the aromatic carbon atoms, the assignment of the quaternary and para resonances were distinguished by their lower intensity compared with the ortho and meta carbons. Distinction between the former pair was achieved by off-resonance decoupling. Ambiguities still remain for the assignments of the C-o and C-m atoms in all cases. However, the lower field resonance was assigned to the ortho position comparable to previous assigned 4-phenyl-4-piperidinols[55,56].

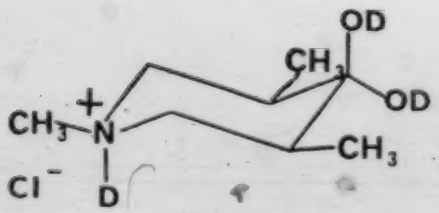
For the γ-isomer and its hydrochloride salt the absence of symmetry gives rise to equally intense resonances for all of the ring carbon atoms. Off-resonance and modulated off-resonance techniques enabled distinction of C-4, the quaternary carbon atom and the methyl, methylene and methine carbons. The actual assignments were made through consideration of substituent parameters and trends observed upon protonation as described by Jones and co-workers[43,55,56].

DISCUSSION

Comparison of the carbon-13 chemical shifts of 1,3,5-trimethyl-4-piperidone and 1,3-dimethyl-4-piperidone[55] enables determination of the substituent effects of the equatorial methyl group (α + 3.1 ppm, β + 8.1 ppm). These values compare favourably with those determined by Jones and Hassan[43] (+3.7 and +7.9 ppm, respectively) for piperidine rings. The β-effect of the equatorial methyl on the carbonyl resonance causes a downfield shift of 2.9 ppm. This difference in β-effects was also

noted by Jones and Hassan and attributed to the compensating effect of the carbonyl oxygen atom.

The pmr spectrum of the 4-piperidone hydrochloride salt was determined in both $CDCl_3$ and D_2O. In the former, the N-methyl signal appeared as a doublet (J_{HH} = 7 Hz) centered at 2.9_3 ppm and the ring methyl appeared as a doublet (J_{HH} = 6 Hz) centered at 1.0_9 ppm. In the latter there was no change in the ring methyl shift but the N-methyl was a singlet at 3.1_1 ppm due to deuterium exchange of the N-H proton with the solvent. A further example of coupling of the N-methyl signal in $CDCl_3$ solvent was observed in the pmr spectra of the α, β and γ hydrochloride derivatives (Table III). The carbon-13 spectrum of the hydrochloride 17a determined in D_2O gave duplicate resonances for C-2,6, C-3,5 and C-3',5' carbon atoms. The "new resonances" accounted for about 10% of the total concentration and are attributable to the 4,4-dideuteroxy form of 17a since a concomitant resonance was observed at 93 ppm typical of a dihydroxy substituted carbon (C-4). Other examples



17a

of hydration of the C-4 carbonyl group has been reported by Casy and Hassan[91] for the hydrochloride salt of 1,2,5-trimethyl-4-piperidone.

TABLE III

Proton Chemical Shifts[a] and Coupling Constants[b] of the N-Me and C-Me Protons in the α, β and γ Free Bases and Hydrochlorides

	N-Me	C-Me
α	2.3_0	0.5_7 (6.0 Hz)
α·HCl	2.8_5 (5.0 Hz)	0.6_7 (5.5 Hz)
β	2.3_9	0.6_3 (6.5 Hz)
β·HCl	3.0_4 (4.5 Hz)	0.7_8 (6.5 Hz)
γ	2.2_7	0.7_6 (6.5 Hz) eq; 0.8_2 (7.3 Hz) ax.
γ·HCl	2.8_3 (5.0 Hz)	0.9_0 (4.5 Hz) eq; 1.1_0 8.0 Hz) ax.

[a] Given in ppm downfield from TMS. Solvent $CDCl_3$.

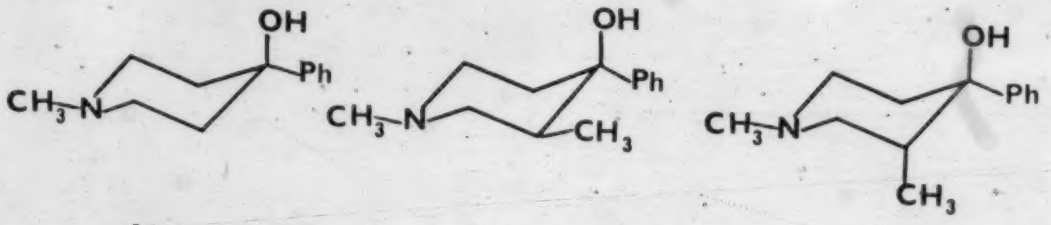
[b] Values in parenthesis.

The configuration of the α-isomer is identical to that proposed by Sorokin. The single resonance at 12.2_4 ppm characterises the equatorial ring methyl groups[56]. The C-q aromatic carbon at 145.6_0 ppm compares with the equivalent carbon in the α-isomer of 1,3-dimethyl-4-phenyl-4-piperidinol[55] (147.5 ppm) if one considers the additional γ-shielding effect of the C-5 methyl group. In the 1,3-dimethyl system the phenyl group is established as having the equatorial orientation.

In the β-isomer the C-3,5 and C-3',5' carbon positions are deshielded by 3.1 ppm and 1.1 ppm, respectively, compared to the α-isomer. Similar effects (+3.0 and +2.4 ppm) were observed at the analogous C-5 and C-5' carbon positions in the β-isomer of the 1,2,5-trimethyl-4-phenylpiperidin-4-ol[56] (12) in which the phenyl group is established as axial. The configuration of the phenyl group is defined by the shift of the phenyl C-q carbon. In the 1,2,5-trimethyl and 1,2-dimethyl-4-phenylpiperidin-4-ols this carbon is shielded by 2.3 and 3.8 ppm, respectively, compared to the isomer where the phenyl group is equatorial. In the 1,3,5-trimethyl, β-isomer the effect is similar in magnitude (-4.0 ppm). The similarity in the effects on the phenyl C-q carbon in the 1,2- and 1,3,5-isomers suggests similar conformations for these compounds. The attenuated value in the 1,2,5-isomer is attributed to a change in the relative orientation of the phenyl ring (vide infra). There is a noticeable difference in the substitution effects between the axial hydroxyl and axial phenyl groups on the C-2 and C-6 carbons in the 1,2-isomers; +1.4 and +0.2 ppm, respectively (axial phenyl has C-2 and C-6 to low field). However this cannot be attributable to methyl substitution since the analogous effect in the 1,3,5-isomer at C-2,6 is +1.4 ppm. Similar shieldings occur in the 1,2,5-isomer, +2.5 ppm (C-2)

and +0.4 ppm (C-6) with an enhanced effect at C-2 compared to the 1,2-isomer. It is suggested that the difference in the deshieldings at the C-2 and C-6 positions in the 1,2- and 1,2,5-isomers is due to the relative orientation of the phenyl ring with respect to these carbons. The deshielding being due to a δ-effect caused by the interaction of the C-2 and C-6 carbons with the C-o aromatic carbons. The enhanced deshielding at C-2 in the 1,2,5-isomer is attributable to a change in phenyl orientation so as to cause a greater interaction between the C-o and C-2 carbons. The δ-effect also accounts for the deshieldings of the C-5' methyls in the 1,2,5- and 1,3,5-isomers mentioned earlier.

The assignment of the γ-isomer was aided by the empirical additivity relationships derived from compounds 10a and 11a(α), i.e. α + 2.4, β_{C-q} + 3.3, β_{C-2} + 7.4 ppm[55] and applied to 11a(β).

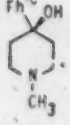
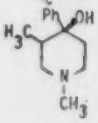
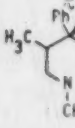
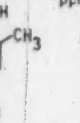
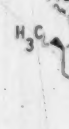
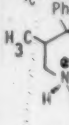
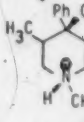
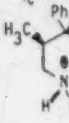
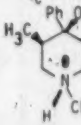


10a 11a(α) 11a(β).

The calculated shifts agree well (Table IV) for the C-4 and C-6 carbon atoms but deviate by 2.4 ppm at C-5. Evidently, there is no α-effect, the shifts in both 11a(β) and γ being 31.50 ppm. This effect presumably arises from a 1,4-gauche interaction between the phenyl ortho carbons on

TABLE IV

The Carbon-13 Chemical Shifts[a] of 1-, 1,3(ax)-, 1,3(eq)-, 1,3(eq),5(eq)- and 1,3(ax),5(eq)-Trimethyl-4-phenylpiperidin-4-ols, their Hydrochlorides and the Derived Equatorial Methyl Additivity Parameters

Carbon Position	Structure[d] and Additivity Parameters[b]												
	10a 	11a(α)[c] 	α 	Δ_{ppm}[b]	11a(β)[c] 	χ 	Δ_{ppm}[b]	11a(α)·HCl[c] 	α·HCl 	Δ_{ppm}[b]	11a(β)·HCl[c] 	χ·HCl 	Δ_{ppm}[b]
C-2	51.6_9	59.0_8	58.9_1	-0.2δ	58.1_4	58.4_8	~0δ	56.3_8	55.8_3	-0.6δ	56.1_7	56.2_1	~0δ
C-3	38.3_6	40.7_9	40.8_3	~0γ	40.2_3	42.1_9	+2.0γ	37.8_2	38.7_9	+1.0γ	39.5_0	41.0_5	+1.6γ
C-4	70.0_9	73.3_8	75.9_6	+2.6β	72.7_0	76.2_8	+3.6β	71.4_9	74.6_1	+3.2β	71.2_2	74.5_0	+3.3β
C-5	38.3_6	39.4_4	40.8_3	+1.4α	31.5_0	31.5_0	0α	37.1_7	38.7_9	+1.6α	28.7_0	30.1_6	+1.5α
C-6	51.6_9	51.6_9	58.9_1	+7.2β	51.5_6	59.4_5	+7.9β	50.8_8	55.8_3	+5.0β	50.6_1	56.2_1	+5.6β
C-1'	46.2_9	46.2_9	46.1_2		46.4_9	46.5_6		43.4_9	43.4_3		44.4_6	44.5_6	
C-Me		12.3_0	12.2_4	-0.1δ	16.2_9	16.6_2(a) 12.8_4(eq)	+0.3δ	11.8_7	11.9_8	-0.1δ	15.5_4	14.5_5 12.5_9	-1.0δ
C-q	149.0_2	147.4_6	145.6_0	-1.9γ	147.2_4	145.4_9	-1.8γ	145.0_0	142.9_6	-2.0γ	144.6_5	143.0_6	-1.6δ

[a] Solvent: $CDCl_3$.

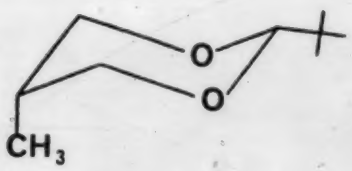
[b] Δ_{ppm}. Additivity Parameters of equatorial methyl.

[c] Reference

[d] Chair conformation, +R, substituent axial, −R, substituent equatorial.

the C-5 position, which effectively compensates for the 'normal' α-effect. The C-1' carbon resonance was assigned by a proton selective decoupling experiment, the chemical shift is identical to that in the 1,3-dimethyl system (11a(β)). Selective decoupling of the ring methyls was not possible due to the small differences in their proton chemical shifts (Table III). However, the 16.6_2 ppm and 12.8_4 ppm shifts are assigned to the axial and equatorial methyl carbons, respectively. The high field shift compares favourably with those in the α-isomer (12.2_4 ppm) and in 11a(α) (12.3_0 ppm)[55]. The low field shift of the axial methyl group is attributed to removal of the hydroxyl group γ-gauche effect which is present in the equatorial methyl substituted compounds. In cis- and trans-2-t-butyl-5-methyl-1,3-dioxanes[92] the identical geometric relationship occurs with the axial C-5' methyl group deshielded (3 ppm) compared to that in the equatorial isomer.

trans-1,3-dioxane



cis-1,3-dioxane

Recently, Eliel and co-workers[34] have described a hyperconjugative-type interaction arising between the free-electron pairs centered on the oxygen atom with the C_α - C_β bond which is accompanied by a subsequent alternation of the electron density at the γ-anti-periplaner carbon, i.e. equatorial methyl, to explain this effect. An identical explanation can be used in the nitrogen compounds to account for the shielding of the equatorial methyl group (11a(α) and (γ)) relative to the axial methyl group (11a(β) and γ).

Two important features arise from the derivation of the additivity effects by comparing the free base and corresponding hydrochloride salt chemical shifts (Table IV). (a) The equatorial methyl β-deshielding effect is attenuated by 2 ppm at the C-6 carbon in the hydrochlorides relative to the free base. Presumably the positive charge on the nitrogen restricts the positive character of the adjacent carbon atom. (b) The γ-effect at C-3 is increased by 2 ppm when the methyl groups are trans orientated in the free base of the γ-isomer compared to the cis-diequatorial methyls of the α-isomer. It is not clear why an axial substituent at the γ-carbon should increase the γ-effect of the equatorial methyl, other model compounds need to be studied.

Comparison of the ring methyl carbon shifts in compounds 17 (Table II), 11a(α) and 11a(β) (Table IV) upon introduction of the equatorial methyl gives the gauche-trans and trans-trans δ effects for the methyl carbons in compound 11a(β) and 11a(α)/17, respectively. The gauche-trans δ-effect is small and deshielding (+0.3 ppm) but in the hydrochloride has a shielding value of -1.0 ppm. This value is quite large in comparison to the values reported in the literature[37] (+0.5 ppm). The trans-trans δ-effect in both 17 and 11a(α) is small and shielding, -0.5 and -0.1 ppm, respectively. As expected[43] protonation of the nitrogen atom results in upfield shifts at all piperidine ring carbons (Table II).

The proton chemical shifts for the N-methyl and ring methyl proton resonances in the α, β and γ free bases and hydrochlorides are given in Table III. The pmr results for the γ-isomer clearly differentiates the axial and equatorial methyls (assigned by magnitude of the coupling constants compared to α- and β-isomers). The hydrochlorides of

all three isomers show coupling between the $\overset{\oplus}{N}$-H and N-methyl protons of approximately 5 Hz.

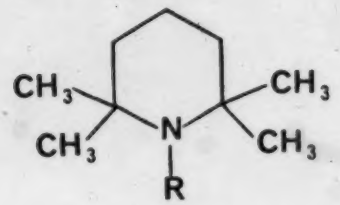
CONCLUSION

The cmr and pmr spectral evidence thus allow unambiguous assignment of the conformations of the three isomers, α-, β- and γ-1,3,5-trimethyl-4-phenyl-4-piperidinol.

B. The Stereochemistry of 1,2,2,6,6-Pentamethyl-4-piperidone and some of its Derivatives

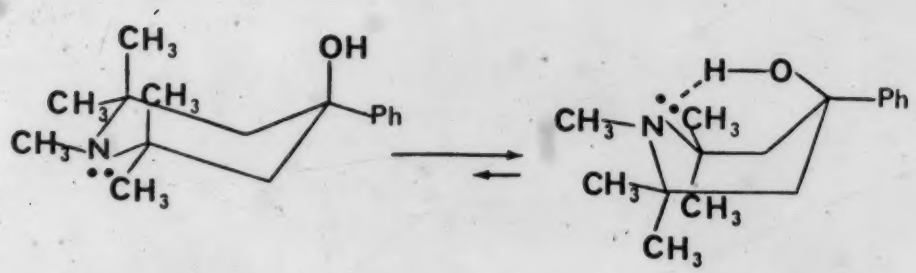
INTRODUCTION

The 2,2,6,6-tetramethylated piperidine skeleton has various pharmacological properties depending on the substituents present on the C-4 carbon position[93]. However, stereostructural-activity relationships have not been reported for these systems. Hence we have studied the 4-oxo and 4-hydroxyl derivatives of 18 and the 4-oxo, 4-hydroxyl and 4-phenyl-4-ol derivatives of 19. The most interesting aspect of the pentamethyl system is the steric congestion about the nitrogen center.



18 R = H; 19 R = CH_3.

Attempts to N-methylate the 4-oxo derivative of 18 with methyl iodide failed even under refluxing conditions. Steric interactions are increased upon introduction of an axial group at the C-4 position. Infrared studies[10] have shown that the equilibrium of the phenylalcohol (2a) lies to the right (2b), the chair form having extreme steric strain due to the



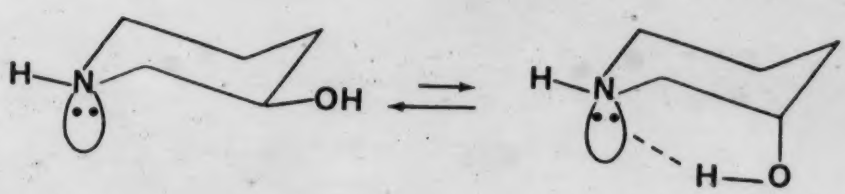
2a 2b

three opposing axial substituents. The attempt to observe the -N···H-O interaction in the above molecule was studied with an emphasis on the possible breakdown of additivity relationships in the proposed non-chair conformation.

Recent independent cmr studies by Jones[94] and Lippman[95] have shown the equivalence of the methyl groups in 2,2,6,6-tetramethyl-piperidine (18). However, owing to different interpretations concerning the use of Grant's additivity parameters[30b], conflicting views of the molecule's conformation have resulted (vide infra). The similar 3,3,5,5-tetramethylcyclohexanone has been subjected to considerable study using pmr[96] and cmr[97] methods. St. Jacques[96] has provided evidence for the chair conformation of this ketone. However, Stothers'[97] results suggest

distortion in this system from the perfect chair. Similar substitution of methyl groups in the 1,3-dioxanes has been investigated by Kellie and Riddell[26]. These authors suggest that the 2,4-syn-axial interaction of methyl groups in the 2,2,4,4-tetramethyl substituted 1,3-dioxanes cause the molecule to prefer a 'deformed chair' conformation. Other workers have studied pmr line broadening effects in N-sulfinyl, -sulfenyl and -sulfonyl derivatives of 2,2,6,6-tetramethyl-4-piperidone[98]. Even with these large bulky groups it was found that nitrogen atom inversion was as rapid for the N-sulfonyl derivative as for N-H and N-Me tetramethyl-4-piperidones. However, the rate was slowed down sufficiently for the sulfenyl and sulfinyl derivatives to allow axial and equatorial methyl groups to be observed.

3-Piperidinol 20 has been shown by I.R.[25] to exist in a form which demands intramolecular hydrogen bonding. The hydroxyl group adopts the sterically less favourable axial orientation 20(b). A pmr



20(a) 20(b)

study[99] has been reported and the estimated mole fraction of conformer 20(a) given as 0.64 when determined in CCl_4, corresponding to a conformational free-energy difference of approximately 0.37 kcal/mole for the 3-hydroxyl at 30°. We have attempted to observe this interaction using

carbon-13 nmr in order to establish the contributions made by intramolecular hydrogen bonding to ^{13}C-shifts.

RESULTS

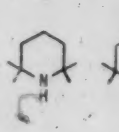
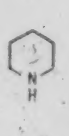
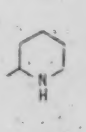
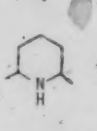
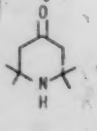
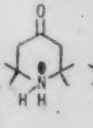
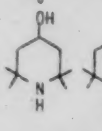
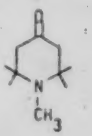
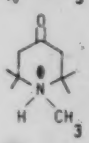
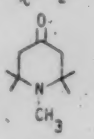
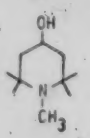
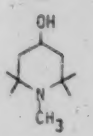
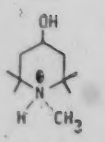
The observed carbon-13 chemical shifts for the N-H and N-methyl 2,2,6,6-tetramethylpiperidin-4-oxo 24 and 26 and 4-ol derivatives 25 and 27 and their corresponding hydrochloride salts along with the supporting data for piperidine, 2-methyl, 2,6-dimethyl and 2,2,6,6-tetramethylpiperidine, (21, 22, 23 and 18) are presented in Table V. Table VI summarizes the ^{13}C chemical shifts for the 1-methyl-(10a), 1,2,6-trimethyl (28) and 1,2,2,6,6-pentamethyl-4-phenylpiperidin-4-ol (2). along with a solvent study for the latter. The protonation effects on these compounds are given in Table VII. Table VIII summarizes the α-, β- and γ-additivity effects arising from introduction of methyl substituents at the C-2 and C-6 positions in a series of piperidines and the C-3 and C-5 positions in cyclohexanone. The effects of solvent variation on the ^{13}C chemical shift of 20 are summarized in Table IX.

The condensation of phorone with aqueous methylamine is well known[100,108]. However the product was always isolated as the free base and then characterized. Instead, in a similar reaction we isolated the product as a hydrochloride and after workup obtained two fractions. Extraction of the crude hydrochloride with chloroform gave one fraction, the remaining material being soluble only in water. We denote these extracts $CHCl_3 \cdot HCl$ and $H_2O \cdot HCl$, respectively (26a - $CHCl_3$, 26a - H_2O). Solvent studies using $DMSOd_6$, CD_3OD, CD_3OH, D_2O and $CDCl_3$ were carried out on the $CHCl_3 \cdot HCl$ extract and D_2O and CD_3OD for the $H_2O \cdot HCl$ extract. These results are summarized in Table X.

Assignments of the carbon-13 resonances to the appropriate

TABLE V

Carbon-13 Chemical Shifts[a] Of 4-Methylene-, 4-oxo- and -4-ol Derivatives of NH and NCH_3 Piperidines

Carbon Position	Compound 18	19	21	22	23	24	24a	25	26	26a·$CHCl_3$	26a·H_2O	27^+	27^*	27a
														
C-2,6	49.7^c (49.6_3)[d]	53.5_3[e]	47.7^c (47.7)[b]	53.7_7[f] (48.2_0)[g]	52.8^c (52.4)[f]	54.8_6	60.0_0	52.4_4	58.7_5	67.0_6	57.5_7	55.3_5	56.4_8	66.1_4
C-3,5	38.9 (38.6_8)	40.8	27.7 (27.5)	35.9_0[g] (27.4_8)	34.7 (34.5)	53.7_8	49.7_5	48.0_7	55.7_2	52.1_1	48.1_8	50.1_2	50.3_3	46.8_2
C-4	18.8 (18.4_0)	17.7	25.7 (25.5)	(26.3)	25.5 (25.4)	210.2_2	208.1_3	64.4_1	209.6_9	202.3_0	210.7_2	63.5_5	63.6_0	60.5_3
C-1'									28.6_4	29.0_8	26.8_2	28.0_5	28.3_6	29.4_0
C-2'6'	32.5 (31.6_7)	27.3		24.0_2	23.5 (23.4)	31.8_3	27.5_8	28.2_7(a) 34.3(eq)	27.3_0	22.6_0(a) 28.6_4(eq)	23.0_4	20.6_1(a) 33.3_4(eq)	21.0_4(a) 33.1_2(eq)	21.5_8(a) 29.4_0(eq)

[a] Solvents: $CDCl_3$: 24, 26, 26a·$CHCl_3$ and 27^*.
CD_3OD: 25, 27^* and 27a.
D_2O: 24a and 26a·H_2O.

[b] Values obtained for $CDCl_3$ solution - J. Leung, Thesis, University of Alberta, 1975.

[c] Taken from Reference 94; solvent C_6D_6: original data converted using $\delta_c^{C_6D_6} = 128.5_4$

[d] Solvent $CDCl_3$.

[e] Calculated values only.

[f] Reference 43; Solvent: Neat.

[g] Top value C-2 and C-3, bottom value C-6 and C-5.

TABLE VI

Carbon-13 Shifts of 1-, 1,2,6(trans)- and 1,2,2,6,6-Methylated 4-phenylpiperidin-4-ols

Carbon Position	Compound / Solvent					
	10a[a]	28[a]	2	2	2[c]	2
	$CDCl_3$	$CDCl_3$	$CDCl_3$	CS_2	$DMSO_{d-6}$	CD_3OD
C-2,6	51.6$_9$	54.8$_6$[b] 47.3$_2$	54.8$_6$	55.3$_1$	55.3$_6$	57.0$_2$
C-3,5	38.3$_6$	43.6$_5$[b] 39.0$_6$	51.8$_9$	51.7$_0$	52.7$_1$	51.4$_6$
C-4	70.0$_9$	73.4$_3$	73.4$_7$	73.2$_2$	73.5$_4$	73.6$_3$
C-2'6'(axial)		13.4$_9$	28.5$_9$	26.0$_2$	23.0$_4$	22.8$_2$
C-2'6'(equat.)		19.8$_6$	29.6$_1$	31.6$_3$	35.5$_6$	32.8$_5$
C-1'	46.2$_9$	46.8$_3$	28.0$_0$	28.4$_4$	29.3$_6$	28.5$_4$
C_q	149.0$_2$	149.3$_5$	148.8$_3$	149.7$_7$	152.7$_3$	150.8$_9$
C_o	128.2$_5$	128.2$_5$	128.1$_2$	128.3$_5$	129.1$_6$	128.7$_7$
C_m	124.7$_4$	124.5$_8$	124.5$_1$	125.0$_6$	126.2$_4$	125.3$_7$
C_p	126.8$_5$	126.7$_9$	126.5$_6$	126.7$_4$	127.4$_3$	127.2$_1$

[a] Reference 55.

[b] Top value being C-2 and C-3 chemical shifts.

[c] Original data converted using $\delta_c^{DMSO_{d6}}$ 41.1$_7$ ppm.

TABLE VII

Protonation Effects on Carbon-13 Chemical Shifts of 1-, 1,2,6(trans)- and 1,2,2,6,6-Methylated 4-phenylpiperidin-4-ols in Certain Solvents

Carbon Position	Compound and Solvent									
	10a[a]	10a[a]·HCl	28[a]	28·HCl[a]	2	2·HCl	2[c]	2·HCl[c]	2	2·HCl
	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$DMSO_{d6}$	$DMSO_{d6}$	CD_3OD	CD_3OD
C-2,6	51.6_9	50.6_1	54.8_6[b] 47.3_2	58.2_2[b] 51.0_4	54.8_6	63.9_8	55.3_6	64.7_5	57.0_2	65.7_1
C-3,5	38.3_6	35.0_1	43.6_5[b] 39.0_6	44.4_6[b] 40.4_1	51.8_9	47.8_0	52.7_1	48.8_3	51.4_6	49.3_1
C-4	70.0_9	67.9_8	73.4_3	71.3_8	73.4_7	72.3_4	73.5_4	72.7_3	73.6_3	72.5_0
C2'6' (ax.)			13.4_9	13.7_0	28.5_9	22.7_6	23.0_4	23.5_3	22.8_2	22.5_4
C2'6' (eq.)			19.8_6	17.1_6	29.6_1	30.1_0	35.5_6	30.9_2	32.8_5	30.5_9
C-1'	46.2_9	43.1_1	46.8_3	37.8_8	28.0_0	28.1_6	29.3_6	29.6_8	28.5_4	29.6_2
C-*o*	149.0_2	146.3_2	149.3_5	147.4_6	148.8_3	147.9_2	152.7_3	150.8_5	150.8_9	149.8_9
C-*o*	128.2_5	128.0_3	128.2_5	128.2_5	128.1_2	128.3_9	129.1_6	129.4_3	128.7_7	129.3_1
C-*m*	124.7_4	124.4_7	124.5_8	124.9_1	124.5_1	124.7_8	126.2_4	126.3_5	125.3_7	125.6_7

TABLE VII (cont'd)

Protonation Effects on Carbon-13 Chemical Shifts of 1-, 1,2,6(trans)- and 1,2,2,6,6-Methylated 4-phenylpiperidin-4-ols in Certain Solvents

Carbon Position	Compound and Solvent									
	10a[a]	10a[a]·HCl	28[a]	28·HCl[a]	2	2·HCl	2[c]	2·HCl[c]	2	2·HCl
C-p	126.8_5	127.0_1	126.7_9	127.0_6	126.5_6	127.2_1	127.4_3	128.1_9	127.2_1	128.1_8

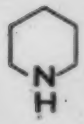
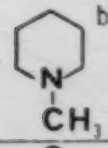
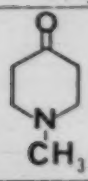
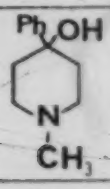
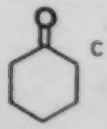
[a] Reference 55.

[b] Top value being C-2 and C-3 chemical shifts.

[c] Data converted using $\delta_C^{DMSO_{d6}}$ 41.1_7 ppm.

TABLE VIII

Additivity Parameters for Introduction of 2,2,6,6-Tetramethyl Substituents To Some Piperidine Derivatives and 3,3,5,5-Tetramethyl Substituent to Cyclohexanone

Compound[a]	Additivity Parameter			
	α	β	γ_{C-4}	γ_{N-Me}
	+2.0	+11.2	-6.9	
 [b]	-3.1	+14.7	-6.2	
	+3.4	+14.8	+2.6	-16.5
	+3.2	+13.5	+3.4	-18.3
 [c]	+8.9	+11.9	$\gamma_{C=O}$ +0.5	

[a] Solvent: $CDCl_3$.

[b] Chemical Shifts of N-methylpiperidine: C-2,6 56.6_9, C-2,5 26.1_1, C-4 23.9_3, N-Me 46.9_4, taken from J. Leung, Thesis, University of Alberta, 1975.

[c] Reference 97.

TABLE IX

Solvent[b] Study of 3-Hydroxypiperidine(20) CMR Shifts[a]

Solvent	Carbon Position C-2	C-3	C-4	C-5	C-6
Dioxane	55.4_4	66.9_9	35.1_0	25.8_8	47.3_5
C_6H_6	54.9_6	67.1_5	34.5_1	25.1_2	47.0_3
CCl_4	55.2_3	67.4_2	34.9_4	25.7_7	47.5_1
CH_3COCH_3	55.0_6	67.5_3	34.6_7	25.5_6	46.9_2
CH_3OH	53.7_7	67.6_4	33.9_2	25.0_2	46.3_3
$CHCl_3$	55.1_2	67.9_0	34.7_3	25.6_1	47.6_2
Pyridine	55.7_7	67.9_0	35.3_2	26.1_0	47.3_0
CH_3SOCH_3	55.9_8	68.2_8	35.8_1	26.8_0	47.5_7
H_2O	53.1_2	68.6_1	33.8_6	25.2_9	46.1_6
Average	54.9_3	67.7_1	34.7_6	25.6_8	47.4_8

[a] External lock C_6D_6 used as reference; original data converted using $\delta_c^{C_6D_6} = 128.5_4$.

[b] 1 molal, sol'n temp. 25°.

TABLE X

Carbon-13 Chemical Shifts of $CHCl_3 \cdot HCl$ and $H_2O \cdot HCl$ In Various Solvents[a]

Solvent	Compound and Carbon Position					
	$CHCl_3 \cdot HCl$					
	C-1'	C-2',6'(ax.)	C-2',6'(eq.)	C-2,6	C-3,5	C-4
$CDCl_3$	29.0_8	22.6_0	28.6_4	67.0_6	52.1_1	202.3_0
CD_3OD	30.3_7	22.4_9	29.1_3	68.8_3	53.0_8	203.3_8
CD_3CN	30.2_6	23.3_5	29.1_8	68.2_9	52.4_5	204.4_5
$DMSO_{d6}$[b]	30.3_8	23.4_8	29.3_0	67.9_8	53.0_9	205.0_6
D_2O[c]	29.9_5	Broad	Broad	67.4_0	51.8_5	206.9_5
	$H_2O \cdot HCl$					
CD_3OD	27.4_6	23.7_9	23.7_9	58.5_3	49.2_5	209.9_6
D_2O[c]	26.8_2	23.0_4	23.0_4	57.5_7	48.1_8	210.7_2

[a] Solution approx. 250 mg/2 mls of solvent.

[b] Original data converted using $\delta_c^{DMSO_{d6}} = 41.1_7$ ppm.

[c] Original data converted using $\delta_c^{Dioxane} = 66.7_4$ ppm.

carbon position in the compounds studied were made using conventional techniques as discussed in Chapter One.

DISCUSSION

1. General Additivity Effects in the 2,2,6,6-Tetramethyl System

The chemical shifts for piperidine, 21 and 2,6-dimethylpiperidine 23, have been reported in the literature[43,94]. Although the determinations were for neat liquids and a solution in C_6D_6, the shifts agree to within 0.5 ppm. Hence solvent effects must be considered minimal. Comparison of 21 with the 2-methyl derivative 22 gives additivity parameters for an equatorial methyl, α + 5.7, β + 8.5 and γ + 0.7 ppm. Analogous parameters derived for 2,6-dimethylpiperdine 23 are α + 4.7, β + 1.5 and γ + 0.7 ppm. The noticeable decrease in the β-effect arises from the fact that the diaxial conformer will only be present to a small extent in 23 due to severe 1,3-diaxial interactions, hence chair to chair interconversion will not be as important for 23 as in 21 and 22. The value 23.4 ppm can be taken as a typical (C-2'6') equatorial ring methyl shift. On further methyl substitution at the 2,6-position, as in 18, the axial and equatorial methyls become equivalent and only one methyl resonance is observed at 31.6_7 ppm ($CDCl_3$). It is expected that the chair to chair interconversion will be rapid since in each chair there exists the same syn-diaxial interactions.

The carbon chemical shifts of 19 were not obtained directly but rather calculated from the additivity effects obtained by comparing 24 and 26; and 25 and 27, (replacing N-H by N-Me) the average additivity parameters are α + 3.9, β + 2.1, γ_{C-4} - 0.7 and γ_{C-Me} - 4.4 ppm.

Applying these parameters to 18 enables calculation of the chemical shifts in 19. Carbonyl group substituent parameters were derived by comparing 18 and 24. (α + 15.1, β + 5.2 and $\gamma_{C\text{-}Me}$ + 0.2 ppm). Consideration of the carbonyl effect on the calculated shifts in 19 provides data for 26. The calculated and observed shifts in 26 are in excellent agreement [C-2,6 (0.0), C-3,5 (0.2) and C-2',6' (0.2 ppm)].

Table VIII gives the additivity effects arising from introduction of gem-dimethyl substituents in a series of piperidine ring systems and cyclohexanone. The β-effect remains constant in all of the compounds while the α-effect is greatly attenuated upon introduction of an electronegative nitrogen (compare the substitution of phosphorus, Chapter Four). For the N-methyl and N-H piperidines the γ-effect is shielding, while substitution at the C-4 position by a carbonyl or phenylalcohol group causes a deshielding γ-effect. Introduction of carbonyl for methylene at C-4 removes the readily polarizable C-H bond that is attributable to the shielding γ-effect. Deshielding in the phenylalcohol derivative is due to a conformational change from a chair (10a) to a non-chair in the pentamethyl derivative (2). (vide-infra) A similar deshielding was reported[55] for comparison of 28 and 10a where introduction of an axial C-2' methyl deshields C-4 (+3.3 ppm). The α-effect in the tetramethyl substituted systems is deshielding except in the N-methylpiperidine (-3.1 ppm). This shielding effect cannot be explained at this time.

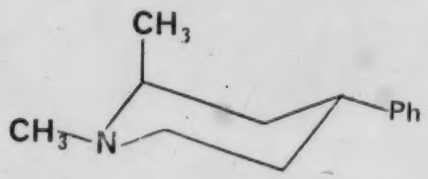
2. Specific Conformational Effects

a. 2,2,6,6-Tetramethylpiperidine Derivatives

As mentioned earlier additivity parameters derived by

Dalling and Grant[30b] have been used to predict the carbon-13 chemical shifts in 18. However, the conformation of this molecule is still in doubt. Jones et al.[94] suggests a twist structure based on the calculated and observed chemical shift discrepancies (shown in parenthesis), C-2,6 (10.0 ppm), C-3,5 (5.8 ppm) and C-4 (5.4 ppm), while Stothers[102] using Lippmaa's[95] results reports that similar shieldings to those in the methylcyclohexanes operate. From this statement Lippmaa's results might be interpreted in terms of a chair conformation undergoing rapid chair to chair interconversion. The discrepancies quoted by Stothers, C-2,6 (0.2 ppm), C-3,5 (2.5 ppm) and C-4 (3.7 ppm) appear to be significant. It has been reported by Jones[43] that the N-methylpiperidines warrant a different set of additivity parameters from those of the methylcyclohexanes.

We have derived the C-2'6' axial methyl parameter from the reported[103] chemical shifts of 29 and 30 and calculated shieldings for



29

30

18 based on the values for 23. The calculated chemical shifts of 18, together with the discrepancies (shown in parentheses) from the observed shifts, are C-2,6, 42.3 (7.3), C-3,5, 37.7 (1.0) and C-4, 20.1 ppm (1.7 ppm), respectively. Although these values are in better agreement

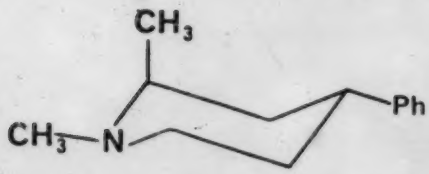
than those derived by Jones[94] the large discrepancy for C-2,6 must be considered indicative of distortion in this molecule from a perfect chair. Our interpretation thus supports the skew-boat structure.

The methyl resonances for the the tetramethyl piperidine 18 absorb 9.0 ppm (C_6D_6 data) downfield compared to those in the dimethyl analog 23. This shift difference is identical to that observed between the 3,5 and 3,3,5,5 methylated cyclohexanones[97]. This value is attributed to the β-effect of the axial methyl upon the equatorial methyl groups and a deshielding syn-axial δ-effect for the axial methyls. A concomitant γ-shielding effect of -6.6 ppm occurs at the C-4 position in 23 upon introduction of the axial methyls.

Introduction of a carbonyl group at C-4 in 18 has no effect on the ring interconversion and the methyl resonances remain equivalent. The α-carbonyl substituent effect is +15.1 ppm in agreement with the value +14.7 ppm reported by Jones and Hassan[43]. The solid state conformation of this piperidone (24) has been described as a distorted chair. However, similar evidence for a chair conformation in the analogous 3,3,5,5-tetramethyl cyclohexanones has been reported[104]. Clearly the solid-state X-ray crystalographic data and the solution studies for these systems cannot be compared.

Introduction of an hydroxyl group at the C-4 position as in 25 inhibits interconversion between equivalent conformers. The hydroxyl group prefers the equatorial configuration to avoid the steric interaction with the axial C-2'6' methyl carbons. The additivity parameters for introduction of the equatorial hydroxyl, 25, are in agreement with those for the analogous N-methyl-4-piperidinol[94] (α + 42.6, β + 8.9 and γ - 2.7 ppm) which is established as preferring the chair conformation.

Hence a similar chair conformation is suggested for 25. The axial and equatorial methyl carbon atoms in 25 are assigned to the resonances at 28.2_7 and 34.3_1 ppm, respectively. The assignment of the upfield resonance to the axial methyl follows from protonation of 1,2,2,6,6-pentamethyl-4-piperidinol 27, in which introduction of an axial proton would produce a γ-gauche interaction at the equatorial methyl carbon and hence shielding (-3.7 ppm). The N-H proton and axial methyl are anti to each other and consequently little or no effect is expected at the methyl carbon (+0.5 ppm). Analogous effects are observed in 1,2,6-trimethyl-4-phenyl-piperidin-4-ol (28)[55], trans-1,2-dimethyl-4-phenyl-piperidine (29)[103] and 1,2,6-trimethylpiperidine (31)[55].



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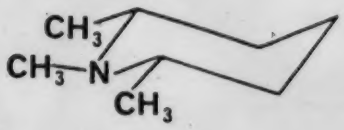

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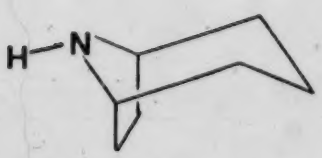
It has been postulated[44] that the protonation effect may have some stereospecific nature, the protonation-induced shifts of the γ-carbon atoms falling in the order θ = 0°(cis) > θ = 180°(trans) > θ = 60°> θ = 120°. However, from the results cited above the order for θ = 180, θ = 60° should be reversed, θ = 60° > θ = 180°. The present results are more consistent with the change in charge density obtained by the

pseudo-atom approach, i.e. $\theta = 0°$(cis) > $\theta = 60°$ > $\theta = 180°$(trans) > $\theta = 120°$ (Figure 4).

b. 1,2,2,6,6-Pentamethylpiperidine and -4-Piperidinol

The calculated shifts of the piperidine 19 have been described earlier along with the implications caused by steric congestion around the nitrogen atom. The additivity parameters, for introduction of an hydroxyl group obtained by comparing 19 and 27 (α, +45.9, β, +9.3 and γ, -1.8 ppm) are similar to those reported by Roberts[105a] (α, +43.2, β, +8.0 and γ -1.1 ppm) for an equatorial hydroxyl group. The equatorial orientation of the hydroxyl group in 27 is thus established.

Comparison of 25 and 27 (changing N-H for N-Me) shows that introduction of an N-methyl group has a large shielding effect (-7.7 ppm) on the axial methyls and only a small shielding effect (-1.0 ppm) on the equatorial methyl carbons. The closest analogy for the former shift is that in the tropane structures 32 and 33[106]. The C-6,7 carbons



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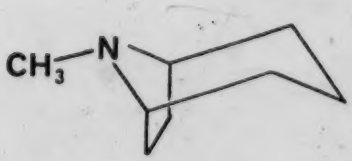

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are axial and are shielded (-3.4 ppm) upon introduction of the N-methyl substituent. Thus, the shielding value (-7.7 ppm) seems exceptionally large. A valid comparison of the equatorial methyl shielding can be

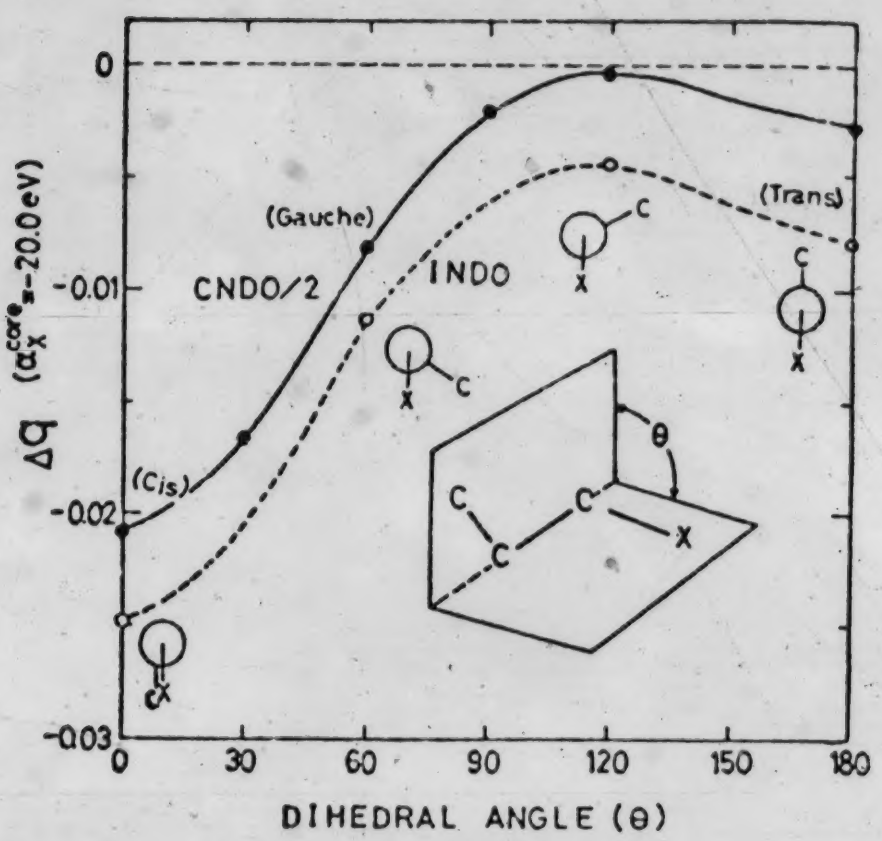


FIGURE 4: Δqc_γ Varying with Dihedral Angle θ[44].

made between 2,6-di and 1,2,6-trimethylpiperidines. Here the equatorial methyls C-2'6' are shielded by 1.5 ppm. In 2- and 2,6-methylpiperidines and their N-methyl derivatives it has been reported[43] that the N-methyl group causes an upfield shift at the ring methyl groups of -2.6 ppm. Similar effects have been established in analogous 1,3-dioxanes[92] and methylcyclohexanes[30b]. The origin of these shifts is thought[43] to be due to steric interactions, the magnitude of the effect being dependent on interatomic distance between the interacting sites. It, therefore, seems likely that the large upfield shift of the axial methyl groups in 27 is due to ring distortion in which the axial methyl and N-methyl distances are pronounceably shorter than in the perfect chair structure.

Protonation of 27 causes familiar upfield shifts for the ring carbons with the exception of the substituted C-2,6 positions (deshielded as predicted[43]). The N-methyl carbon is also deshielded (+1.0 ppm) whereas in other piperidine derivatives this carbon is usually shielded[43,55,56].

c. 1,2,2,6,6-Pentamethyl-4-piperidone

The results for the title compound 26 and its hydrochloride salt require more detailed discussion. The free base and its N-H precursor are freely inverting systems as indicated by the observation of only one methyl resonance in both the pmr and cmr spectra. However, protonation restricts the conformational interconversion and separate carbon resonances are observed for the axial and equatorial methyl groups, 22.6_0 ppm and 28.6_4 ppm, respectively. The shifts are assigned by comparison with the analogous carbon shifts in the 4-piperidinol derivative (27a) (21.5_8 and 29.4_0 ppm). A second hydrochloride (aqueous extract) (26a·H_2O) derivative was isolated for the 4-piperidone in which

the ring methyls were equivalent (23.0_4 ppm).

The pmr of the aqueous extract hydrochloride exhibited three resonances at 1.3_7, 2.5_5 and 2.6_1 ppm. Intergration of these regions showed a 12 to 7 proton ratio. Hence, the upfield region was tentatively assigned to the equivalent methyl groups and the lower resonances to the N-methyl and methylene protons, respectively. The pmr of the chloroform extract gave an AB pattern for the methylene protons with ν_A = 2.4 and ν_B = 3.7 ppm, J_{AB} = 6.5 Hz. The ring methyls absorbed at 1.3_6 and 1.8_0 ppm, the N-methyl resonance occurred as a doublet J_{HH} = 4 Hz, coupled to the N-H proton and centered at 2.8_7 ppm, the N-H proton resonates at 12.3 ppm. Decoupling at the N-H resonance frequency collapsed the N-methyl doublet to a singlet. Similar N-methyl coupled resonances were observed in the hydrochloride salts of 1,3,5-trimethyl-4-piperidone (17) and of the three 4-phenylalcohol isomers, α, β and γ.

The chloroform extract is also soluble in water and its pmr spectrum determined in D_2O gave only two resonances at 2.8_2 and 1.6_2 ppm. These absorptions fall in the center of the N-methyl doublet and the two methyl resonances for the chloroform solution spectrum (see Figure 5). Further, the chemical shifts for the D_2O solution of the $CHCl_3 \cdot HCl$ extract are not the same as those in the $H_2O \cdot HCl$ extract. Spectrum (c) Figure 5, shows the spectrum of the $CHCl_3HCl$ extract after being in contact with water for the (b) spectrum, Figure 5, removing water by rotary evaporation and then determining its spectrum in $CDCl_3$ again. The presence of water clearly results in the N-methyl and ring methyl signals becoming single resonances. The degree of chemical equivalence seems to be dependent on the amount of water present.

The question arises as to the composition of these two extracts.

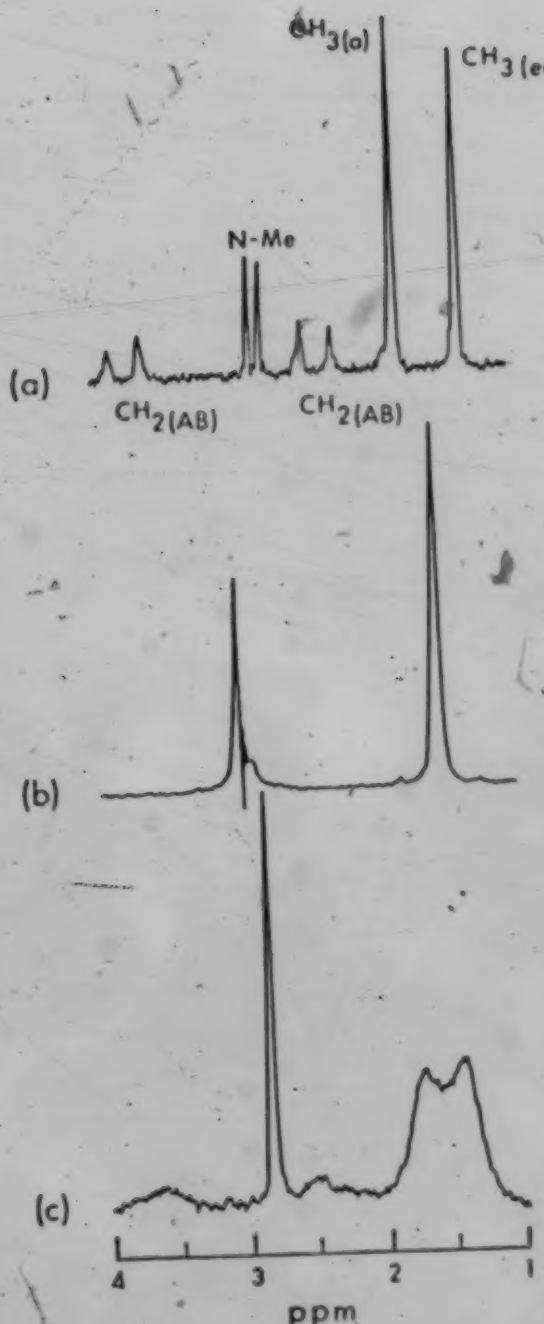


FIGURE 5. Pmr Spectrum of the $CHCl_3$·HCl extract in (a) $CDCl_3$, (b) D_2O, and (c) $CDCl_3$ after being in contact with D_2O.

Both give the same fragmentation pattern in their mass spectra with parent m/e 169 and mass measurements of 169.1468. Basification of both hydrochlorides gives the identical base as shown by the pmr spectra. The infrared spectrum of the $CHCl_3 \cdot HCl$ (nujol) gave a carbonyl band at 1720 cm^{-1} and a $\overset{\oplus}{N}$-H band at 2380 cm^{-1}. The I.R. spectrum of the $H_2O \cdot HCl$ extract (nujol) had an identical carbonyl stretching absorption, but the $\overset{\oplus}{N}$-H band was at higher frequency (2750 cm^{-1}) and additional bands were observed at 2450 and 1590 cm^{-1}. The latter two absorption bands indicate the presence of a water of hydration[107] as in Figure 6. This explains the concomitant shift to higher frequency of the $\overset{\oplus}{N}$-H absorption band, the OH band is weakened whereas reduction of the positive charge on nitrogen, consequent upon this interaction renders the $\overset{\oplus}{N}$H band less polar. A similar observation has been reported[108] for the diastereomeric 1,2-diaryl-4-dimethylamino-3-methylbutan-2-ol hydrochlorides.

Hydrates of the hydrochlorides of similar penta- and tetramethyl compounds have been described in the literature, 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol[10]·HCl, 1,2,2,6,6-pentamethyl-4-piperidinol[53]·HCl and 2,2,6,6-tetramethyl-4-piperidone[104]·HCl all contain water of hydration. The yields of the $CHCl_3$ and H_2O hydrochloride extracts is dependent upon reaction conditions, the longer the reaction time, the more $H_2O \cdot HCl$ extract is obtained. The reaction under anhydrous conditions gave only the $CHCl_3$ extract product.

Carbon-13 data help to further characterize the structures of the $CHCl_3$ and H_2O extracts and allow the identification of the N-methyl and methylene resonances in the latter. The cmr resonances and chemical shifts are consistent with the structures of the free base and hydrochloride of both extracts. The principle difference between the two

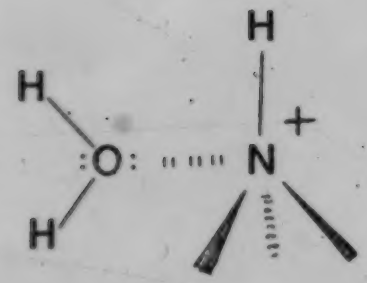


FIGURE 6: Hydrogen bonding between water of hydration and nitrogen.

hydrochlorides is that the aqueous extract gives only a single resonance for the ring methyls. Selective proton decoupling showed that the resonance to high field (2 ppm range) in the pmr spectrum of the free base and hydrochloride of the aqueous extract was due to the N-methyl protons.

A solvent study of the cmr chemical shifts of the $CHCl_3$ extract was made in order to observe solvent effects as portrayed in the pmr spectrum. The results are presented in Table X. The chemical shift data is consistent with solvent polarity, the carbonyl resonance moving downfield in the more polar solvent. The only major solvent effect occurred in D_2O where the ring methyl resonances appear as broad signals, indicating an equilibrating situation. Increasing the temperature to 87° coalesced these signals to a singlet at 25.1 ppm. High temperature studies were undertaken with $DMSO_{d-6}$ and CD_3OD as solvents. No change took place in the former. However, in the latter at 52° the ring methyl resonances began to broaden, the other resonances remaining sharp, indicating an approach to an equilibrating situation. It appears that the $CHCl_3$ extract in protic media undergoes proton exchange with solvent. This exchange is faster with water than with methanol, water being the smaller molecule. This exchange allows ring interconversion and hence equilivalence of the methyl resonances (25.1 ppm). It should be noted that this shift is to low field compared with that in the aqueous extract (23.0 ppm) but is close to the 27.3 ppm value for the interconverting free base. Further evidence for the proton exchange with the solvent is indicated by the pmr spectra. That is, the N-methyl coupling to the NH proton in $CDCl_3$ but not in D_2O.

An explanation for the equivalent ring methyls in the aqueous

extract also involves exchange of the $\overset{\oplus}{N}H$ proton with solvent. The cmr chemical shifts for the $H_2O \cdot HCl$ extract are all at higher field (except C-4) then the $CHCl_3 \cdot HCl$, possibly as a result of the water of hydration causing greater steric interactions. The exceptional high field N-methyl resonance of 26.8_2 ppm suggests a contribution from an axial N-methyl conformer. This possibility also follows from the $\overset{\oplus}{N}H$ exchange argument. For exchange to occur in a finite time the N-methyl group must be at least pseudo-axial in orientation as shown in Figure 7. Interconversion of structure B to A allows for the equivalency of the ring methyl carbons. Structure C is a proposed intermediate, the exchanging of the $\overset{\oplus}{N}H$ proton from the nitrogen to water occurring from either side.

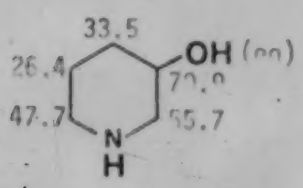
d. 1,2,2,6,6-Pentamethyl-4-phenyl-4-piperidinol

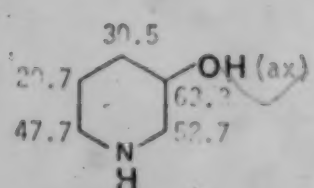
Since a N·····HO interaction has been suggested[10] in the title compound a ^{13}C NMR study on 3-piperidinol, where a similar interaction exists[99], was undertaken in order to observe the effects on the ^{13}C chemical shifts.

i. Intra-molecular Hydrogen Bonding - A Model Study

Solutions of 3-piperidinol were made up in dried solvents at 1 molal concentrations. All nmr determinations were carried out at 25°C. In order to avoid inter-molecular effects chemical shifts were measured relative to an external deuterated benzene reference.

The following chemical shifts were calculated using additivity effects for axial and equatorial hydroxyl groups[105] on the piperidine





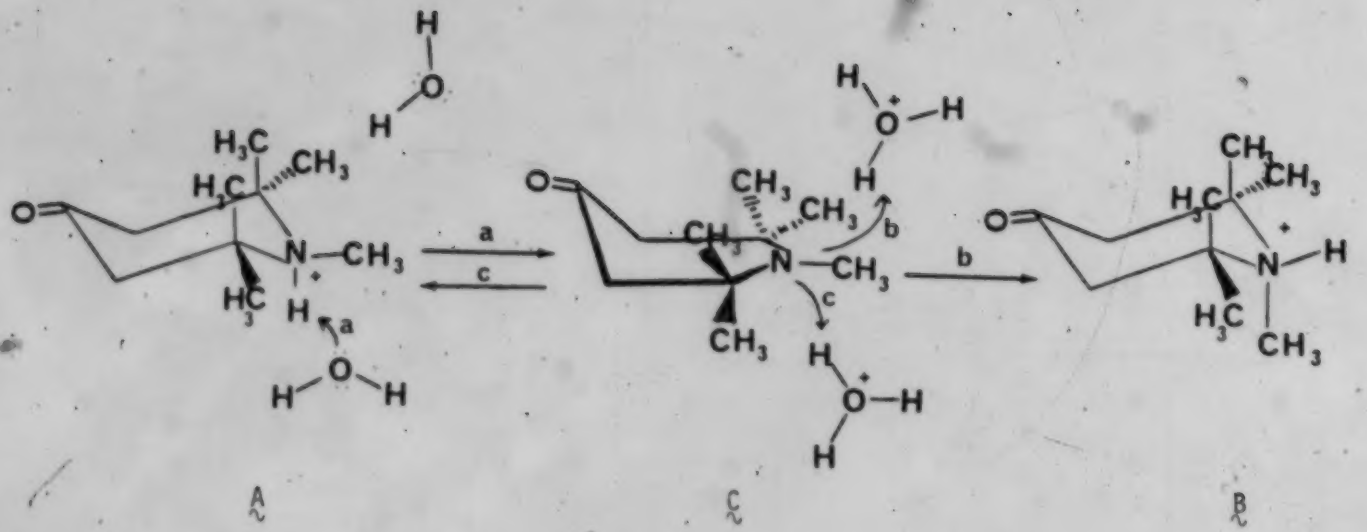


FIGURE 7: Proton exchange between N-H and solvent (H_2O).

ring. These values and the mole fractions obtained in the pmr studies[99] (n(eq) = 0.64 for equatorial OH) were used to calculate the expected carbon-13 chemical shifts for an equilibrated solution from the relationship[109].

$$\delta_{obs} = n_a\delta_a + n_{eq}\delta_{eq}.$$

The following chemical shift values arise C-2:54.6, C-3:68.2, C-4:32.4, C-5:24.3, C-6:47.7 ppm. Discrepancies compared with the observed values (CCl_4, Table IX) are C-2:+0.6, C-3:-0.8, C-4:+2.5, C-5:+1.5 and C-6:-0.2 ppm.

Table IX lists the solvents used in this study in order of increasing polarity. The only consistent change in chemical shifts occurs at the C-3 carbon. As the polarity increases this carbon shifts to lower field indicating a larger contribution from the equatorial conformer since the equatorial hydroxyl conformer has the C-3 chemical shift at 7.6 ppm to lower field than the axial conformer.

One molal solutions were used for these experiments and hence inter-molecular hydrogen bonding effects cannot be ruled out. Therefore, we also studied 0.2m and 0.1m solutions under the same conditions. Similar chemical shifts were obtained. Infrared spectra were determined for all concentrations of solution ($CDCl_3$ free of ethanol). The 1 molal solution exhibited a broad hydrogen bonded OH band at 3280 cm^{-1} and a very small free OH band at 3600 cm^{-1}. The latter increased in intensity upon dilution to 0.2m. In carbon tetrachloride the 0.1 molal solution exhibited a free-OH band at 3600 cm^{-1} and a broad band for hydrogen bonded-OH at 3300 cm^{-1}, the latter being resolved into two bands on dilution to 0.02m, at 3520 cm^{-1} (OH·····N-) and 3360 cm^{-1} (N-H). From

these data it can be concluded that a significant amount of inter-molecular hydrogen bonding is present at the high concentrations (1m and 0.1m), while at lower concentrations (0.02m) intra-molecular hydrogen bonding is evident. Because of the concentration limitations inherent to cmr measurements the chemical shifts are averaged values and the information obtained from I.R. (0.02m) cannot be duplicated.

We must, therefore, conclude that direct measurement of intra-molecular hydrogen bonding using ^{13}C nmr measurements is not likely to be valuable unless large conformational changes occur in the molecular system. giving rise to additional features, additivity breakdown, steric γ-gauche effects, etc. These approaches were used in the pentamethylpiperidinol, 2 (vide-infra) and various tropane derivatives (Chapter III).

d. 1,2,2,6,6-Pentamethyl-4-phenyl-4-piperidinol (cont'd).

The conformation of the phenylalcohol, (2) was first investigated by an infrared study. The I.R. of 2 determined in carbon tetrachloride (5×10^{-2} M) exhibited a sharp band at 3590 cm^{-1} and a broad band at 3300 cm^{-1}. The solution used for the ^{13}C spectral determinations (approximately 1 molal) also showed these absorptions. Thus, it is apparent that the molecule remains in a similar environment in both dilute and concentrated media.

Comparison of cmr data for the free base in a variety of solvents (Table VI) showed a marked solvent dependency especially at the C-2,6 and C-2',6' positions. The analogous pmr results are given in Table XI. These results show that the methylene protons in these solvents are equivalent since a characteristic AB pattern is not observed.

TABLE XI

PMR Solvent Study of 1,2,2,6,6-Pentamethyl-4-phenyl-4-piperidinol

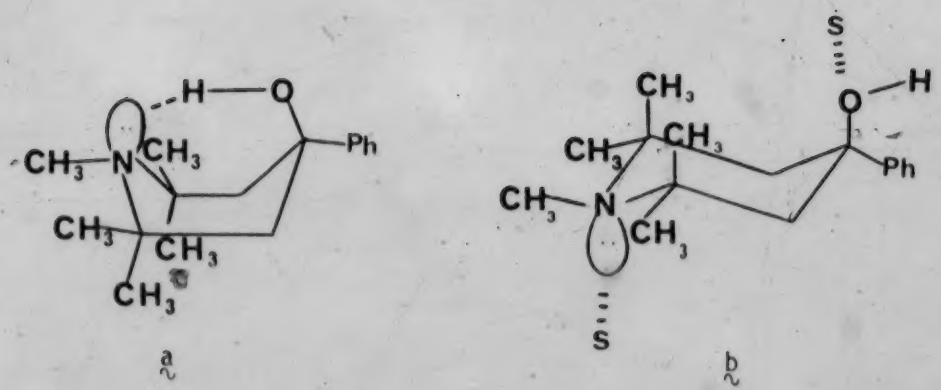
	CS_2	$CDCl_3$	CD_3OD
N-Me	2.2_8	2.3_5	2.4_0
CH_2	1.8_2	1.9_8	1.9_0
CH_3(eq)	1.1_4	1.2_1	1.1_8
CH_3(a)	1.2_8	1.3_5	1.4_0
Phenyl	7.0-7.4	7.3-7.6	7.2-7.6

Instead, a broad signal is observed for these nuclei. The broadest signal was observed in the hydrochloride salt, then the free base in methanol, the sharpest in deuterochloroform. These results confirm that the molecule is in a non-chair conformation with the methylene protons (in the free base) less equivalent in the more polar solvent (CD_3OD). Intra-molecular hydrogen bonding will favour a 'pseudo'-boat form as the preferred conformation (Figure 8). As the solvent polarity increases, the amount of intramolecular hydrogen bonding decreases and the orientation of the OH bond will be projected as shown in Figure 8b, binding with the solvent at both the hydroxyl and nitrogen ends of the molecule.

The change in the orientation of the hydroxyl group is reflected at the C-2,6 carbon positions, structure b in Figure 8, having a smaller γ-effect at these carbon atoms. The carbon C-2,6 is at lowest field (57.0_2 ppm) in CD_3OD and highest field (54.8_6 ppm) in $CDCl_3$. The 2.1 ppm difference suggests a change in the conformation in these solvents. More dramatic solvent shifts are noticeable at the C-2'6' carbon atoms. However, the carbon-13 chemical shift assignment for the axial and equatorial methyl groups need to be clarified. Thus in compound 27 (determined in methanol) the axial and equatorial methyl carbon shifts are 21.0_4 ppm and 33.1_2 ppm, while the shifts in 2 (determined in methanol) are 22.8_2 and 32.8_5 ppm, respectively. The introduction of the syn-axial hydroxyl in 2 is expected to deshield the axial methyls via a δ-effect. Compared to 27 this equatorial phenyl group will cause

27

2



a ~ b ~

FIGURE 8: Representation of intra-molecular hydrogen bonding in a non-polar solvent (a ~) and solvation (b ~) in a polar solvent (S).

very little perturbation of the ring methyls[103]. By using the published[55] equatorial phenyl additivity parameters we calculated the ring carbon chemical shifts for the compound below. Due to the axial hydroxyl group, the axial and equatorial methyl carbons would be expected to resonate at 22.7 and 33.3 ppm, respectively.

Comparison of these shifts with those for the equatorial hydroxyl (27) provides evidence of γ-gauche shielding effect (-6.3 ppm) on the C-2,6 carbon atoms.

The similarity of the carbon shifts for the axial and equatorial methyls of 2 in $DMSO_{d-6}$ and CD_3OD indicates comparable conformations in these solutions (Figure 8b). However, when CS_2 and $CDCl_3$ are employed as solvents a large deshielding of the axial and shielding of the equatorial methyls is observed. The difference between the axial and equatorial methyl shifts are 5 ppm and 1 ppm, respectively, which should be compared with the difference 12 ppm and 10 ppm for solutions in $DMSO_{d-6}$ and CD_3OD, respectively. Taking the methyl shifts of 22.7 and 33.3 ppm as fixed axial and equatorial values (above) an average value of approximately 28.0 ppm can be determined for a freely flipping situation. Thus the 28-29 ppm shift observed for the methyl resonances of 2 in $CDCl_3$ solution is close to both the equatorial and average value. An equilibrating system is discounted for by the IR data. Thus, we suggest that in chloroform the four methyl groups must be near equatorial. A feature which can only be achieved in a skew structure. Comparison of the

chemical shifts of the ring methyl carbons of the hydrochlorides of 2 determined in $CDCl_3$, $DMSO_{d-6}$ and CD_3OD show similar values, approximately 22.7 and 30.5 ppm for the axial and equatorial carbons, respectively. Hence the same preferred conformations exist in all of these solvents. The shifts for the free bases then cannot be reconciled on the basis of a solvent effect but rather must be due to a conformational change from a chair in CD_3OD solution to a skew-boat in $CDCl_3$.

CONCLUSIONS

The cmr study of the 3-piperidinol to detect intra-molecular hydrogen bonding indicated that a strained molecular system must be chosen in order for cmr to detect any conformational change arising from such an interaction. These constraints were present in the 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol and a skew-boat conformation is suggested for this structure in deuterochloroform solution, the molecule undergoing solvent dependent conformational changes in the solvents investigated. In all the pentamethylpiperidines studied non-chair conformations were found. The conformations were assigned as a consequence of protonation effects and in some instances breakdown in additivity parameters. Two fractions were obtained for the hydrochloride derivative of 1,2,2,6,6-pentamethyl-4-piperidone. One contained water of hydration which showed equivalency of the axial and equatorial methyl groups both in its pmr and cmr spectra determined in D_2O (insoluble in chloroform). The other, determined in $CDCl_3$ solution, gave separate resonances for these methyl groups and when determined in D_2O evidence for an approach to an equilibrating situation was presented.

The significance of lone-pair deshielding via the anti-periplanar

argument was reinforced by observation of the carbon chemical shift parameters of the α- and γ-isomers of 1,3,5-trimethyl-4-phenyl-4-piperidinol. The γ-protonation effects observed in the pentamethylpiperidines should encourage further study on the conformational dependence of the ^{13}C shifts induced by N-protonation.

EXPERIMENTAL

3-Hydroxypiperidinol, 2,2,6,6-tetramethyl-4-piperidone hydrochloride and 2,2,6,6-tetramethyl-4-piperidinol were obtained from Aldrich Chemical Company. A sample of 2,2,6,6-tetramethylpiperidine was donated by Dr. S. Brown. The remaining compounds were prepared by literature preparations with some modifications. In these cases the boiling points and melting points are uncorrected.

1,3,5-Trimethyl-4-phenyl-4-piperidinol (α-isomer)

The procedure as outlined by Sorokin[89] was followed and this product isolated as a white solid; m.p. 130-131°, m.p. (lit.)[89] 131.5-132° IR (Nujol) 3220 cm^{-1} (OH str), Mass. Spec. parent m/e 219.

1,3,5-Trimethyl-4-phenyl-4-piperidinol (β-isomer)

The procedure as outlined by Sorokin[89] was followed with the modification that the isolation of the title compound was carried out by column chromatography of the mother liquor remaining after the maximum amount of the α-isomer was removed by crystallization. Chromatography on alumina; eluting with $CHCl_3$ followed by methanol. The residual α-isomer was eluted by the $CHCl_3$ and the β-isomer by methanol; m.p. 117-121°, m.p. (lit.)[89] 121-121.5°, IR (Nujol) 3300 cm^{-1} (OH str), Mass. Spec. parent m/e 219.

1,3,5-Trimethyl-4-phenyl-4-piperidinol (γ-isomer)

The procedure as outlined by Sorokin[89] was followed with the modification that the isolation of the title compound was carried out by column chromatography. After the maximum amount of α-isomer was isolated through crystallization the residue was subject to column chromatography on alumina eluting with Skelly 'B' benzene 1:3, 4 x 100, then benzene, chloroform 3:1, 4 x 100, 3:1.5, 4 x 100, 1:3, 4 x 100. With the latter solvent system 3 bands separated. The first was eluted and subjected to further column chrpmatography on alumina, eluting first with Skelly 'B' to remove 'impurities' then with chloroform to isolate the title compound. M.p. 130-135°, m.p. (lit.)[89] 134.5-135°, IR (Nujol) 3300 cm^{-1} (OH str). Mass. spec. parent m/e 219.

The hydrochlorides of all three isomers were prepared as outlined by Sorokin[89].

	M.p. Observed	M.p. Reported
α·HCl	221-223°	222-222.5°
β·HCl	222-224°	223-225.5°
γ·HCl	240-241°	241-242°

1,2,2,6,6-Pentamethyl-4-piperidone and hydrochlorides

To 69.1 g (0.5 moles) of freshly distilled phorone (Aldrich) 17.5 mTs of methanol and 60 mls of 40% aqueous methylamine (excess) was added with stirring, the temperature being kept below 40° by slight cooling. The mixture was heated at 60° for 2 hours and the excess methylamine removed under reduced pressure. The solution was acidified with concentrated HCl, the solvent removed by rotary evaporation and a thick oily residue remained. Addition of acetone afforded brownish crystals, extraction with hot chloroform and removal of solvent gave

brown crystals which after several recrystallizations from acetonitrile gave white prismatic crystals of m.p. 185-187°, I.R. (Nujol) 1720 (c=ν str) and 2380 cm^{-1} (NH str). Mass spec. parent m/e 169, [exact mass..169.1468 (measured), 169.1467 (calculated) correct for $C_{10}H_{19}NO$] Pmr CH_3(s) 1.3_6 and 1.8_0 ppm. N-methyl(d) 2.8_7 (J_{HH} 4 Hz). CH_2: AB ν_A 2.4 ppm, $_B$ 3.7 ppm, J_{AB} 6.5 Hz. Solvent $CDCl_3$ ref. TMS. Identified as the hydrochloride of the title compound.

To this residue after extraction with hot chloroform water was added and the solution filtered. The filtrate was removed by rotary evaporation affording white crystals which after several recrystallizations from a mixture of hot acetonitrile and 95% ethanol afforded white crystals of m.p. 169-170°.

I.R. (Nujol 1720 (c=ν str) 2750 (NH str) and 1590 and 2450 cm^{-1} (H_2O of hydration).

Mass spec. parent m/e 169, [exact mass. 169.1468 (measured), 169.1467 (calculated) correct for $C_{10}H_{19}NO$] Pmr CH_3(s) 1.3_7 ppm N-methyl (s) 2.55 ppm CH_2(s) 2.61 ppm. Solvent D_2O ref. TMS (ext). Identified as the hydrochloride of the title compound.

The free bases from both extracts were generated by dissolving the hydrochloride in a minimum amount of water and adding Na_2CO_3 to a pH of 8.5, extraction with chloroform afforded the title compound. B.p. 100° at 15 mm. lit.[101] 122° at 23 mm. Mass spec. m/e 169.

Pmr. CH_3(s) 1.18 ppm, N-methyl (s) 2.3_5 ppm, CH_2(s) 2.40 ppm.

1,2,2,6,6-Pentamethyl-4-piperidinol

A mixture of 2.4 g (14 m moles) of 1,2,2,6,6-pentamethyl-4-

piperidone, 1 g of $LiAlH_4$ in 150 mls dried THF was stirred under a N_2 atmosphere and gently refluxed for 2 hours. Addition of water to destroy excess $LiAlH_4$, filtered, extraction with ether, dried over $MgSO_4$ and the solvent removed afforded a yellow liquid which crystallized on cooling. Recrystallization from Skelly 'B' gave white needlelike crystals, m.p. 73-74°, 1.5 g (62.5%). Sublimation of product gave no further purification. M.p. (lit.)[53] 72.8-74°. I.R. spectrum (film) 3270 cm^{-1} (OH str).

1,2,2,6,6-Pentamethyl-4-phenyl-4-piperidinol

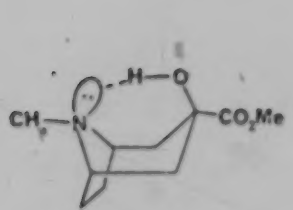
A solution of phenyllithium was prepared from 1.3 g (0.18 moles) of Li and 9.4 mls of freshly distilled bromobenzene in 250 mls of ether. 5.1 g (0.03 moles) of 1,2,2,6,6-pentamethyl-4-piperidone in 50 mls of ether was added slowly. After the addition the solution was stirred and kept under an argon atmosphere overnight. On the following day, the solution was refluxed for 1 hour, cooled, 10 mls of benzene was added and the mixture decomposed with 35 mls of water. The ether-benzene layer was separated, the water layer extracted with ether, the extracts combined and dried over $MgSO_4$. The solvent was removed on a rotary evaporator. The product was a thick oil which failed to crystallize. Phenyl impurities were present and were removed by isolating the hydrochloride, extraction into the water then basifying with NaOH 5% to yield the free base devoid of impurities. I.R. (CCl_4: 5×10^{-3} M) 3300 (H bonded OH) and 3590 cm^{-1} (free OH). Hydrochloride m.p. 229-235°, lit.[10] 235-236°. Mass spec. m/e 247.

CHAPTER III

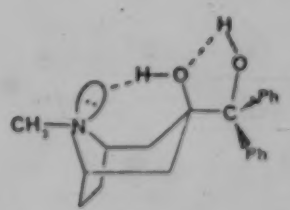
TROPANES

A. INTRODUCTION

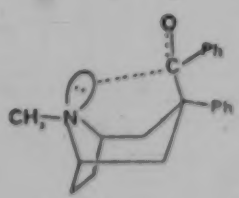
There has been much interest in the pmr spectroscopy of tropane (33) due to the relationship of this bicyclic tertiary base to the classical muscarinic antagonist, atropine (39). Many of these studies have been directed towards determining the preference for the boat or chair conformation in tropine (38). A detailed review is available[110]. Most recently, Casy et al.[24] have observed a preference for the boat conformation in the tropane derivatives 45, 49 and 3. This preference is attributed to strong intramolecular hydrogen bonding interactions in these systems, as shown:



45



49



3

Evidence for the preferred boat conformation in 45, 49 and 3 is based on the coupling between the 1(5)-H and 2(4)-H protons which is broadened in the boat conformer (compared with the chair) as a consequence of eclipsing of these protons. Independent UV studies on 3 also indicate the N·····C·····O interaction[11].

Carbon-13 studies on tropane derivatives have thus far been

limited[106,111]. A minor controversy exists concerning the assignment of the C-2,4 and C-6,7 methylene carbons. The present study resolves this ambiguity and shows that the highest field resonance of the pair attributable to C-2,4 and C-6,7 must be assigned to C-6,7. Further, the reliability of carbon-13 chemical shifts as an index of preferred conformation especially in non-chair hydrogen bonded structures is tested (for other examples see Chapter II). Carbon-13 nmr provides an unambiguous method for the determination of conformation in these systems.

B. RESULTS

For the purpose of clarity, we summarize all known carbon-13 data on the tropanes in the Tables to follow. In Table XII data for the tropane derivatives, 32, 33, 35, 37 previously reported by Wenkert[106] and 38, 39a and 40 reported by Maciel et al.[111] are given. The remaining data was determined in the present work.

Assignment of the carbon resonances was by conventional techniques. Distinction between the methylenes, C-2,4 and C-6,7 is based on comparison with data for protonated 3-tropinone (34a) and N-methylated 3-tropinone (34b) derivatives. The chemical shift of the carbons C-2,4 and C-6,7 are 46.5_1 and 24.9_9 ppm in 34a and 26.3_7 and 26.3_3 ppm in 34b. That is, a larger γ-interaction is apparent at C-2,4 in the N-methyl derivative (34b) due to the steric compression between the protons at this site and the N-methyl group. Conversely, the resonances at 24.9_9 and 26.3_3 ppm are assigned to C-6,7. In all the tropanes the low-field methylene shift is assigned by analogy to C-2,4. Ambiguities remain in the assignment of the quaternary carbon resonances in 36 and 49 and the aromatic carbon resonances in 3 and its

TABLE XII

The Carbon-13 Chemical Shifts of Tropane Derivatives

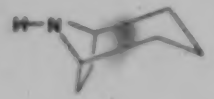
	Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-α	C-β	C-γ	C-δ	C=O	Ester CH_2/CH_3	Reference
32		$CDCl_3$		64.7	32.9	23.0	17.2							106
33		$CDCl_3$	40.4	61.2	29.9	25.6	15.9							106
36		$CDCl_3$	38.4_6	60.9_6	47.6_9	27.9_4	208.2_3							Present
34a		D_2O	39.0_7	63.2_9	46.5_1	24.9_9	206.9_5							Present
34b		D_2O	51.4_7(a) 45.1_1(eq)	69.2_2	26.3_8	26.3_3	208.2_3							Present
35		$CDCl_3$	38.6	59.8	30.7	25.3	166.9							106

TABLE XII (cont'd)

The Carbon-13 Chemical Shifts of Tropane Derivatives

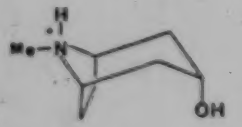
	Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-q	C-o	C-m	C-p	C=o	Ester CH_2/CH_3	Reference
36		$CDCl_3$	40.1_4	60.9_6	38.0_4	25.5_7	$^9(64.5_2)^d$	139.9_9	128.0_7	126.8_8	126.8_8			Present
37		$CDCl_3$	39.2	60.1	38.3	26.7	62.7							106
38		[a]	39.2_4	64.3_3	25.5_7	37.8_3	59.9_8							111
38		$CDCl_3$	40.3_0	60.2_6	39.4_3	26.0_0	63.8_2							Present
38a		D_2O	39.1_1	62.0_4	37.4_4	24.8_7	62.0_4							Present
39		$CDCl_3$	40.2_4	59.6_6	36.2_5	25.2_8	67.0_9							Present

TABLE XII (cont'd)

The Carbon-13 Chemical Shifts of Tropane Derivatives

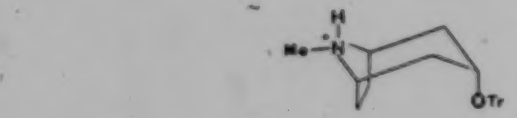
Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-$\underline{i}$	C-$\underline{o}$	C-$\underline{m}$	C-$\underline{p}$	C=O	$C_{\frac{Ester}{CH_2/CH_3}}$	Reference
39a 	D_2O	39.2_2	62.3_1	34.4_6	23.7_3	66.5_0							Present
39a	a	39.5_7	63.0_3 62.9_2	24.0_3 23.7_6	35.2_6 35.0_9	66.4_3							111
40	a	53.4_2	53.7_5	25.2_0	58.2_6 58.0_5	64.4_2							111
39b	D_2O	51.5_4(a) 44.8_5(eq)	68.1_0	25.2_7 25.0_5	32.3_9	64.5_4							Present
41	$CDCl_3$	40.5_1	59.8_8	36.7_9	25.8_9	68.1_3	132.8_1	130.9_8	129.4_7	129.9_0	165.8_3		Present
41a	D_2O	39.4_3	62.3_6	34.7_9	24.7_1	65.3_2	133.5_2	129.3_6	128.7_9	129.3_6	165.3_5		Present

TABLE XII (cont'd)

The Carbon-13 Chemical Shifts of Tropane Derivatives

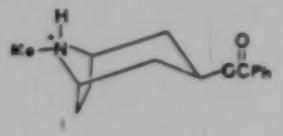
	Compound	Solvent	N-Me	C-1,5-	C-2,4	C-6,7	C-3	C-q	C-o	C-m	C-p	C=o	$^{C}\frac{Ester}{CH_2/CH_3}$	Reference
42		$CDCl_3$	38.7_3	60.3_7	35.8_7	26.7_0	67.8_6	132.7_1	129.5_3	128.2_8	129.9_6	165.3_5		Present
42a		D_2O	38.9_1	63.8_3	35.4_5	24.4_5	65.6_6	134.4_5	130.0_2	129.2_4	129.6_4	167.4_0		Present
43		$CDCl_3$	39.4_3	64.2_5	37.1_2	24.9_2	33.6_1	142.5_3	128.8_2	127.8_0	127.1_0			Present
43		D_2O	38.9_0	64.5_8	37.2_3	24.0_2	32.1_6	143.2_3	129.1_6	127.3_8	127.3_8			Present
44		$CDCl_3$	39.1_1	62.9_0	32.5_8	24.2_2	29.6_1	( )	128.6_6	126.3_4	126.3_4			Present
44		D_2O	38.4_2	63.1_3	33.0_7	23.4_8	29.5_2	( )	128.6_7	126.7_8	126.5_1			Present

TABLE XII (cont'd)

The Carbon-13 Chemical Shifts of Tropane Derivatives

Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-q	C-o	C-m	C-p	C=o	^{C}Ester CH_2/CH_3	Reference
45	$CDCl_3$	39.2_7	58.8_0	41.4_8	27.1_9	71.6_9					174.7_9	52.3_3	Present
45	$MeOH-d_4$	38.5_7	60.8_0	39.7_6	25.6_8	71.5_9					175.6_0	52.7_6	Present
45a	$CDCl_3$	37.7_6	62.0_4	38.2_5	24.0_6	69.7_0					173.4_4	53.0_8	Present
45a	$MeOH-d_4$	38.2_5	63.6_0	39.2_7	24.0_6	69.9_1					174.5_7	53.3_5	Present
46	$CDCl_3$	40.3_0	60.9_1	45.4_8	25.6_8	72.6_7	150.5_5	128.0_7	124.6_7	126.5_6			Present
46	$MeOH-d_4$	40.5_7	62.2_0	46.0_2	25.9_4	72.9_9	151.8_1	128.7_2	125.6_4	127.0_4			Present

TABLE XII (cont'd)

The Carbon-13 Chemical Shifts of Tropane Derivatives

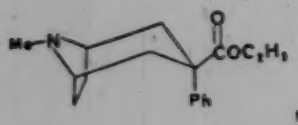
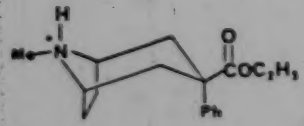
Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-q	C-o	C-m	C-p	C=o	[c] Ester CH_2/CH_3	Reference
46a	$MeOH-d_4$	39.6_5	64.2_0	44.7_8	25.1_9	71.9_6	150.0_8	129.0_9	125.8_0	127.8_0			Present
46a	D_2O	38.8_5	63.6_7	43.0_0	23.4_7	70.9_5	147.4_4	128.8_9	124.5_7	127.7_5			Present
47 	$CDCl_3$	39.8_1	59.0_2	41.4_8	28.2_1	46.0_7	142.5_8	128.1_2	126.7_2	126.6_1	175.3_8	60.3_7 14.2_4	Present
47	$MeOH-d_4$	39.7_0	60.5_3	40.1_4	27.2_4 ( )		142.7_4	128.9_3	127.6_9	127.6_9	176.9_4	61.5_0 14.2_4	Present
47a 	$CDCl_3$	38.7_3	62.9_0	33.9_3	22.9_8	44.7_8	138.5_9	128.5_5	126.7_7	127.7_4	173.3_8	61.3_3 13.7_0	Present
47a	$MeOH-d_4$	38.7_9	64.2_5	35.2_8	23.3_0	45.8_0	139.6_1	129.4_2	127.9_6	128.6_6	175.0_0	62.3_1 13.9_7	Present

TABLE XII (cont'd)

The Carbon-13 Chemical Shifts of Tropane Derivatives

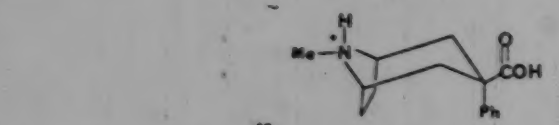
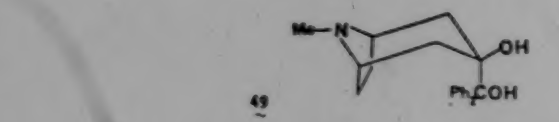
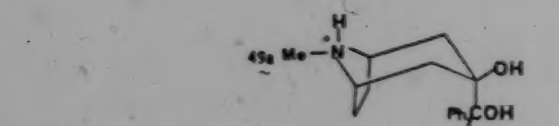
Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-q	C-o	C-m	C-p	C=o	^{C}Ester CH_2/CH_3	Reference
48	MeOH-d_4	38.6_0	64.4_4	36.4_4	23.0_6	47.5_0	141.4_0	129.1_2	127.5_5	127.8_2	168.4_5		Present
48a 	MeOH-d_4	38.9_7	64.0_6	35.0_4	22.9_0	46.9_6	138.8_2	129.2_8	127.6_1	128.5_8	177.8_1		Present
48a	D_2O	38.2_1	63.1_8	34.5_3	22.2_3	44.8_4	138.3_8	128.9_4	127.1_6	128.1_8	177.8_7		Present
49 	$CDCl_3$	40.0_3	58.9_1	41.9_7	28.9_7	(75.6_5)	145.0_6	128.2_8	127.2_6	126.5_0		C-3' (80.1_1)	Present
49	MeOH-d_4	40.4_0	60.0_4	42.5_6	29.4_5	(77.1_4)	(146.6_3)	129.5_2	127.7_4	126.9_9		C-3' (80.3_7)	Present
49a 	MeOH-d_4	39.2_6	62.6_8	40.4_6	28.3_8	(76.1_7)	(145.0_1)	129.3_6	128.6_6	128.0_7		C-3' (80.9_2)	Present

TABLE XII (cont'd)

The Carbon-13 Chemical Shifts of Tropane Derivatives

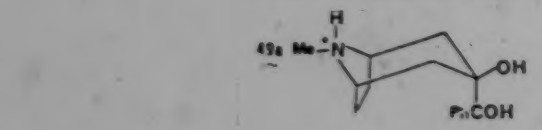
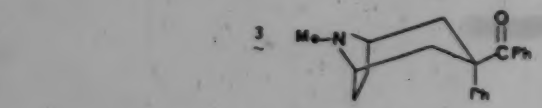
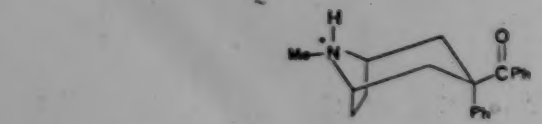
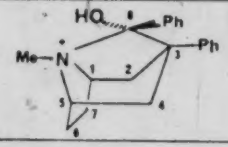
Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-q	C-o	C-m	C-p	C=o	[a]Ester CH_2/CH_3	Reference
49a 	D_2O	38.7_4	61.1_8	39.1_7	27.2_0	(74.8$_8$)	(142.8$_6$)	128.1$_8$	128.1$_8$	128.1$_8$		C-3' (80.8$_2$)	Present
3	$CDCl_3$	39.4_9	58.1_0	44.8_3	29.2_9	50.3_9	(141.8$_8$) (141.6$_8$)	(128.9$_8$) (128.4$_5$)	(127.4$_7$) (127.1$_5$)	(126.6$_1$) (127.1$_5$)	202.6_2		Present
3 	CD_2Cl_2	39.7_0	58.4_2	45.2_6	29.6_7	50.6_1	(142.4$_2$) (142.2$_0$)	(129.2$_0$) (128.7$_2$)	(127.7$_4$) (127.4$_8$)	(126.8$_8$) (127.4$_8$)	202.6_7		Present
3	MeOH-d_4	39.9_5	59.6_5	41.1_1	27.4_0	52.4_0							Present
3a 	$CDCl_3$	38.7_3	63.4_4	35.9_3	22.9_8	50.0_1					202.4_1		Present
3a	MeOH-d_4	39.0_0	64.5_7	37.0_6	23.5_2	(f)					(f)		Present

TABLE XII (cont'd)

The Carbon-13 Chemical Shifts of Tropane Derivatives

	Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-q	C-o	C-m	C-p	C=o	[c] Ester CH_2/CH_3	Reference
3b		$MeOH-d_4$	37.0_6	(C-1) 67.3_8 (C-8) 74.8_2	(C-2) 40.3_0 (C-4) 44.4_0	C-6 30.5_9 C-7 26.5_4	C- 52.6_0					C-8 109.4_1		Present

[a] Solvent not reported.

[b] tr ≡ -C(=O)-C(H)(CH$_2$OH)-φ

[c] High field resonance (CH_3); low field resonance (CH_2).

[d] Parenthesis indicate some uncertainty in assignment.

[e] An equilibrium mixture.

[f] Not observable due to low concentration of this fraction.

[g] Resonance C-3' 66.0_3 ppm.

hydrochloride 3a and 3b.

C. DISCUSSION

1. Additivity Effects

The preferred conformation of the tropane ring is a chair[106]. Introduction of a carbonyl at C-3 as in (34) results in an α-carbonyl substituent effect at C-2,4 of -17.2 ppm which is larger than observed in the piperidines[43] (-14.7 ppm) and cyclohexanes[105b] (-13.4 ppm). This may be due in part to the rigidity in the tropane system. Both axial and equatorial hydroxyl substituent parameters may be derived by comparing the carbon chemical shifts in 33, 37 and 38 determined in $CDCl_3$. The values are: equatorial: α, +46.8; β, +8.4; γ, -1.1 and $\delta_{C-6,7}$ +1.1 ppm; axial: α, +47.9; β, +9.5; γ, -0.9 and $\delta_{C-6,7}$ +0.4 ppm. Of greatest significance is the similarity between the α- and γ-effects for the different hydroxyl configurations. The analogous effects differ widely in cyclohexanes[105a] (equatorial: α, +43.2 and γ, -1.1 ppm; axial: α, +37.8 and γ, -6.8 ppm) as well as in piperidines. (equatorial[94]: α, +42.6 and γ,-2.7 ppm, axial[55]: α, +28.1 and γ, -4.7 ppm). It is possible that there exists a contribution of the boat form in 38 due to severe 1,3-diaxial interactions in the chair conformer. Further, comparison of the C-6,7 carbon resonances in 37 and 38 indicates an hydroxyl δ-shielding of 0.7 ppm in contrast to the deshielding effect expected (2.6 ppm)[37]. These data suggest contributions from the boat conformer of 38. Equatorial phenyl substituent parameters are obtained from comparison of 38 and 46, α, +9.1; β, +6.4 and γ, +1.1 ppm. Compared with the analogous parameters obtained in 4-phenylpiperidines[55], α, +17.7, β, +6.7 and γ, -0.3 ppm, a large decrease in the α-effect is observed.

The contributions from the boat conformer in 38 may again account for these parameters differing. Introduction of the ethylene bridge to the piperidine ring induces the carbon-13 chemical shifts given in Table XIII. The α-effect of +7.0 ppm in piperidine can be taken as the representative value for the introduction of the ethylene bridge with the attentuation to +4.5 and +4.9 ppm in N-methylpiperidine and N-methyl-4-piperidone, respectively, due to the steric interaction of the ethylene bridge with the N-methyl group. The large α-effect of +9.2 ppm in N-methyl-4-phenyl-4-piperidinol may be attributable to the axial hydroxyl group. The β-effects remain questionable under any circumstance. The γ-effect on C-4 of -8.0 ppm can be taken as a representative value with the shielding being greatly attenuated in N-methyl-4-piperidone (+0.2 ppm) as expected. The deshielding γ-effect of 2.6 ppm in N-methyl-4-phenyl-4-piperidinol may be attributed to the axial hydroxyl group. The γ-effect at the N-methyl group has an average value of -6.5 ppm.

2. Tropane Conformations

a. Protonation Effects

In order to determine the conformation of the tropanes both their free base and protonated forms were studied. The protonation effects are summarized in Table XIV.

It is well established[112,113,114] that 3-phenyl-3-tropinol 46 and its corresponding hydrochloride 46a exist preferentially in the chair conformation. Consequently "chair" protonation effects in the tropane system can be determined using this compound as a model, i.e., $\beta_{N\text{-}Me}$ -0.9, $\beta_{C\text{-}1,5}$ +2.0, $\gamma_{C\text{-}2,4}$ -1.2, $\gamma_{C\text{-}6,7}$ -0.8 and $\delta_{C\text{-}3}$ -1.0 ppm. However, if the tropane ring exists in a boat conformation in the free

TABLE XIII

Additivity Effects of the Introduction of the C-6,7 Ethylene Bridge to the Piperidine Ring System

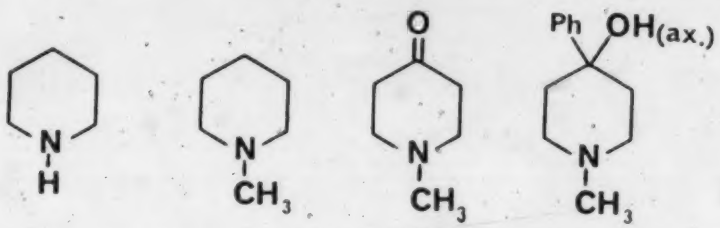
Effect	Structure 			
α	+7.0	+4.5	+4.9	+9.2
β	+5.4	+3.8	+6.2	+7.1
γ_{C-4}	-8.3	-8.0	+0.2	+2.6
γ_{N-Me}	-	-6.5	-7.5	-6.0

TABLE XIV

Protonation Effects on the Carbon-13 Chemical Shifts in Various Tropanes

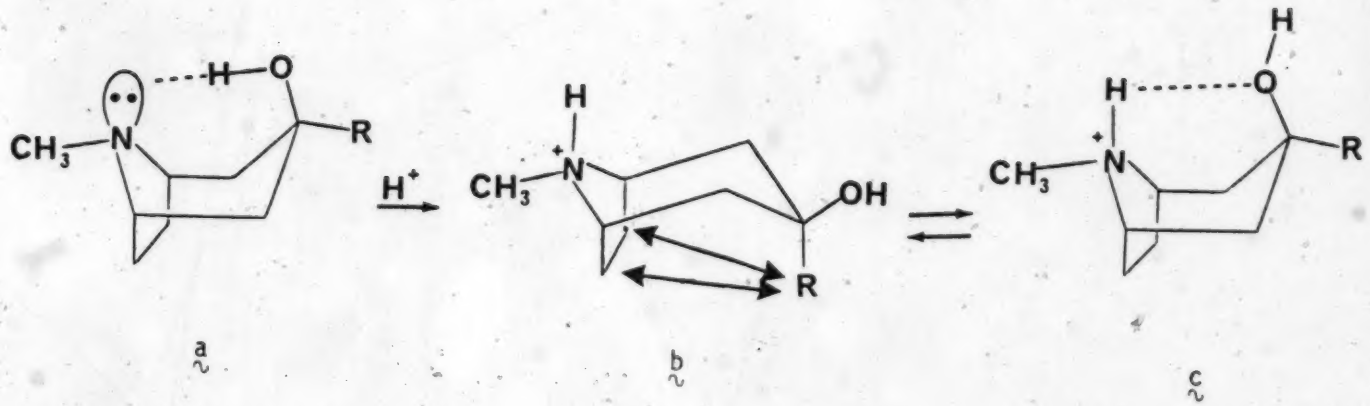
Compound	Solvent	Carbon Position and Effect				
		β(N-Me)	β(C-1,5)	γ(C-2,4)	γ(C-6,7)	δ(C-3)
45	$CDCl_3$	-1.5	+3.2	-3.3	-3.1	-2.0
47	$CDCl_3$	-0.1	+3.9	-7.6	-5.3	-1.3
3	$CDCl_3$	-0.8	+5.3	-8.9	-6.3	-0.4
45	MeOH-d_4	-0.3	+2.8	-0.5	-1.6	-1.7
46	MeOH-d_4	-0.9	+2.0	-1.2	-0.8	-1.0
47	MeOH-d_4	-0.9	+3.7	-4.9	-3.9	
48	MeOH-d_4	+0.4	-0.4	-1.4	-0.2	-0.5
49	MeOH-d_4	-1.1	+2.6	-2.1	-1.1	-1.0
Average values		-0.7	+2.9	-3.7	-2.8	-1.1

base and protonation induces a conformational change different protonation effects are expected.

The major effect upon protonation in this situation will be to produce a γ-shielding effect at C-6,7 in the protonated chair conformation (Figure 9b) as a result of interaction with the added axial C-3 substituent. Any deviations from this γ-effect are expected to reflect a change from preferred chair (Figure 9b) to preferred boat conformer (Figure 9c) in the protonated tropane molecule. A shielding effect at C-1,5 is also expected in the boat conformer, the consequence of eclipsing between the 1(5) and 2(4) hydrogen atoms. Therefore, referring to Figure 9, if the chair conformation (Figure 9b) predominates in the protonated form a relief of the hydrogen interactions will produce an increased deshielding of the C-1,5 carbon atoms compared to those in the protonated boat conformation (Figure 9c). Utilizing these protonation aspects, the tropane conformations can be discussed.

i. Ecgonine Methyl Ester (45)

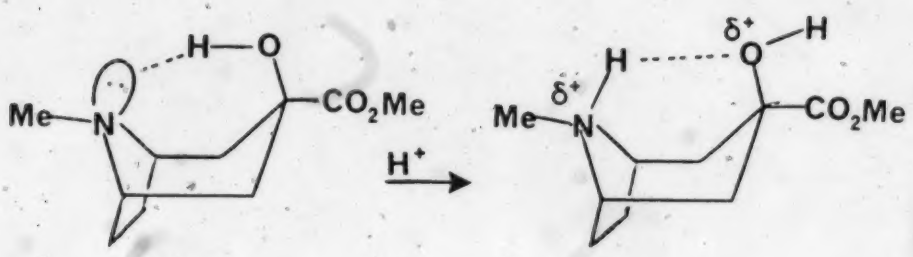
Both pmr and infrared spectral data provide evidence[24] that in solution the boat conformation of 45 is significantly populated. Therefore, the protonation effects observed in the carbon-13 spectrum of 45a refer to the protonated boat conformer of the free base 45 (Figure 9a). These effects are small (Table XIV) and no γ-effect (as discussed earlier) is observed. As far as the carbon-13 results are concerned the magnitude of the protonation effects are not large enough to invoke a conformational change (Figure 9b) but rather a change in the orientation of the hydroxyl O-H bond with concomitant intra-molecular hydrogen bonding between the N-H proton and oxygen is indicated. The boat



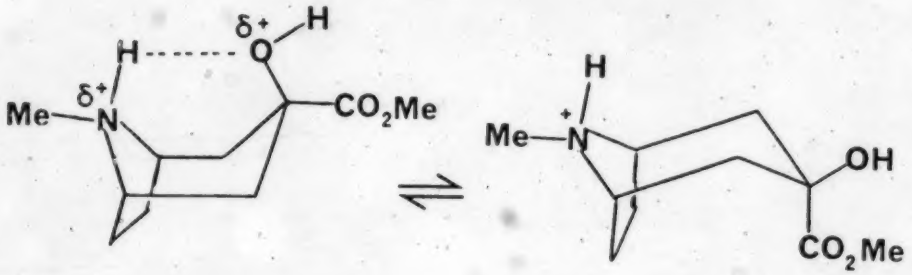
a b c

FIGURE 9: Suggested conformational aspects on protonation of a tropane molecule existing in a preferred boat conformation in a (free base) and c (hydrochloride) due to the intramolecular hydrogen bonding nature of the hydroxyl group.

structure is thus maintained. Comparison of the effects of protonation



of 45 for solutions in methanol-d_4 and chloroform-d_1 show that much larger protonation effects occur in the less polar solvent. In particular, C-6,7 is shielded -3.1 ppm and -1.6 ppm in $CDCl_3$ and MeOH-d_4, respectively, indicating a contribution from the chair conformer of 45a in the former solvent. That is, a γ-shielding effect occurs at C-6,7. It is suggested that the protonated species (45a) be represented by the equilibrium: the boat conformer is favoured in methanol and the chair

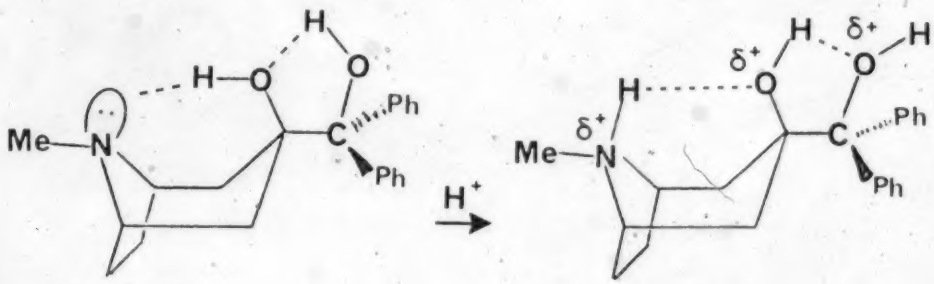


conformer in chloroform. The methanol, being more polar, is better able to solvate the partially charged centers at the nitrogen and oxygen atoms. The chemical shifts observed for the hydrochloride are, therefore,

average values. The protonation effects of 45 in chloroform are explained as follows. The deshielding (+3.2 ppm) at C-1,5 is attributed to a greater amount of 'formal charge' on the nitrogen when in the chair conformer than the boat conformer where the charge is expected to be delocalized over both the nitrogen and oxygen atoms. In addition, the interaction between the eclipsed hydrogens are relieved. The shielding effect (-3.3 ppm) at C-2,4 is a result of both a change in conformation to the chair conformer together with the presence of a more pronounced γ-effect of the $\overset{\oplus}{N}$-H proton.

ii. 3α-Diphenylhydroxymethyl-3β-tropanol (49)

The effects of protonation in 49 can be explained in a similar manner with intra-molecular hydrogen bonding possible in the hydrochloride (49a) with the boat form predominating. The larger

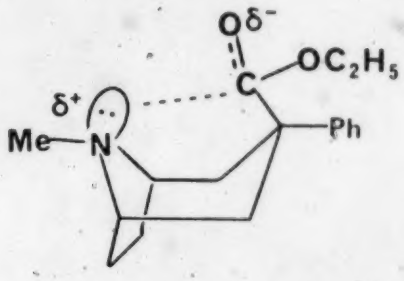


protonation effect (-2.1 ppm) at C-2,4, compared to that in 45 (-0.5 ppm), can be attributed to a difference in the equilibria for the hydrochlorides 49a and 45a. The chair form is dominant in the former resulting in the 2.1 ppm shielding at C-2,4 as a result of a γ-effect of the $\overset{\oplus}{N}$-H proton.

iii. Ethyl 3α-phenyltropane-3β-carboxylate (47)

The hydrochloride of 47 studied in methanol shows large

protonation effects at C-1,5 (+3.7 ppm), C-2,4 (-4.9) and C-6,7 (-3.9 ppm). The pmr study[24] did not indicate any boat structure for this molecule. However, the ^{13}C data indicate contributions from the boat conformer in the free base (47). This can be explained in two ways.

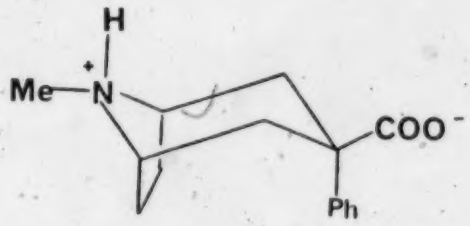


47

First, the large increase in protonation effects from 46 to 47, which should be of similar magnitude if chair forms existed in both structures, can only be explained if a conformational change occurred between the free base and hydrochloride derivatives of 47. The acid derivative (47a) is expected to be predominately in the chair form since no intramolecular hydrogen bonding of the type found in 45 and 49 is possible. Hence the large protonation effects must be due to a change to the chair conformer in 47a with shielding at C-6,7 and deshielding at C-1,5. A large shielding (4.9 ppm) at C-2,4 in 47 also occurs upon protonation and is attributed to the conformational change in addition to the expected γ-effect. Second, the similarity in the magnitude of the protonation effects in 47 and 3. The boat conformation of the latter base is established[11], thus similar conformations for 47 and 3 are indicated.

iv. 3α-Phenyltropane-3β-carboxylic acid (48)

Based on the protonation effects observed in the carbon-13 spectra, a Zwitterion is proposed for the free base 48. This proposal

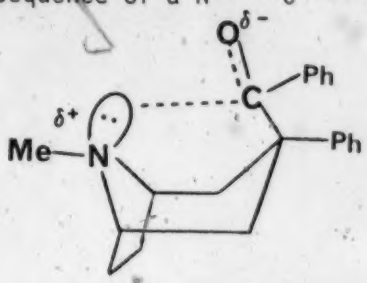


48

is based on the small chemical shift differences observed upon protonation at all the carbon positions except at C-8 (+9.3 ppm) and C-2,4 (-1.4 ppm). The large deshielding at C-8 is due to a change from the carboxylate anion in the zwitterion (48) to the protonated form in the acid (48a). The shielding at C-2,4 is due to a change in the γ-effect, on those carbon atoms, of O^- to OH upon introduction of the proton.

v. 3α-Phenyl-3β-tropanyl phenyl-ketone (3)

The large protonation effects (C-1,5 +5.3, C-2,4 -8.9 and C-6,7 -6.3 ppm) observed in 3 indicate a change in conformation in the compound. It is established that the free base, (3) exists in a boat conformation as a consequence of a N·····C·····O interaction:



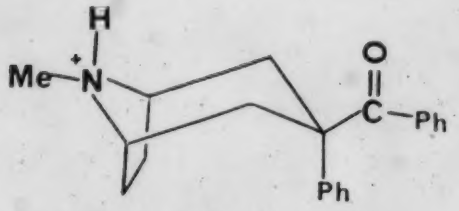
3

Therefore, a chair conformer (Figure 9b) is expected in the hydrochloride (3a) since the possibility of intra-molecular hydrogen bonding as in 45a and 49a is not possible in 3a due to the substituents at C-3 being unable to form a stable intra-molecular hydrogen bonded molecule. Therefore, a change in conformation from a boat conformer in the free base to a chair in the hydrochloride is invoked. As already stated, no conformational changes are evident in 46 upon protonation, therefore, if we assume solvent effects are minimal, subtraction of the protonation effects for 46 from the average values for 47 and 3 give values for the conformational differences in 47 and 3. That is, N-Me, +0.5, C-1,5, +2.5, C-2,4, -7.0, C-6,7, -5.0 and C-3, 0.0 ppm for going from a boat conformer to a chair conformer. The major effects are as expected. C-1,5 is deshielded (2.6 ppm) as a consequence of removal of the eclipsing hydrogen, C-6,7 is shielded (5.0 ppm) due to the introduction of the steric interaction of the C-3 axial substituent and C-2,4 is shielded (7.0 ppm) due to the introduction of a γ-gauche interaction at these carbon atoms with the $\overset{\oplus}{N}$-H proton.

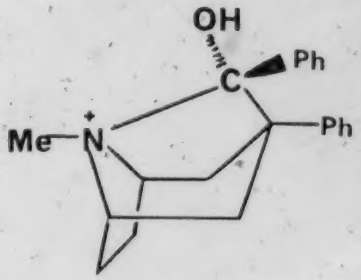
The effect of solvent change on the spectral behaviour of the N·····C·····O interaction in 3 should be noted. The carbon chemical shifts are similar in both $CDCl_3$ and CD_2Cl_2. However, when MeOH-d_4 was used as solvent large chemical shift differences are observed. C-1,5 and C-3 are deshielded (+11.5 and +2.0 ppm, respectively) and C-2,4 and C-6,7 are shielded (3.7 and 2.3 ppm, respectively) the N-methyl resonance is unaffected compared to the chemical shifts determined in $CDCl_3$. The behaviour of 3 in methanol is a result of a greater degree of nitrogen-carbonyl interaction in this solvent than in $CDCl_3$, the methanol being better able to stabilize, by an appropriate solvation

mechanism, the partial charge separation which is produced by this interaction. A similar agrument has been used to explain the change in UV absorption of 3[11].

Similar solvent effects occur for the hydrochloride of 3. In methanol large chemical shift differences arise. Bell and Archer have suggested[11] that this hydrochloride, in methanol, is a mixture which consists mainly of the form with 'formally bonded' nitrogen and carbonyl function (3b) in equilibrium with the form possessing the normal ketone 3a. This is verified in the carbon-13 spectra by the occurrence of the



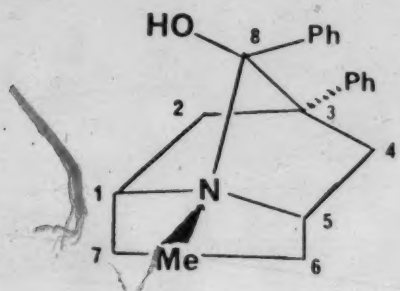
3a



3b

resonance at 109.4$_1$ ppm due to C-8, now an hydroxyl carbon, and also by the I.R. spectra which exhibits absorption bands at 3400 cm^{-1} and 1675 cm^{-1} attributable to hydroxyl and carbonyl functions, respectively. The assignment of the carbon resonances in 3a/3b was facilitated by a change in the equilibrium concentration between two spectral determinations. The chemical shifts of 3a are similar to those obtained for the solution in $CDCl_3$ (<1 ppm difference) and enable assignment of the shifts due to the chair conformation in the equilibrium mixture. The formation of the $N\text{-}C_8$ bond generates an assymetric center at C-8. Hence each carbon in the molecule 3b gives rise to an individual resonance. Structure 3b

can be represented as a norbornyl derivative:



Unfortunately the carbon chemical shift of the analogous norbanyl system without the ethylene bridge have not been reported. Therefore, the distinction between the methine and methylene carbons is based only on the assumption that the hydroxyl group will exert a larger γ-shielding effect at C-1 and C-2 compared to C-5 and C-4.

D. CONCLUSIONS

This study of tropane derivatives successfully clarifies the assignments of the methylene carbons, C-2,4 and C-6,7 and provides a better insight into the conformations of several tropane systems. Carbonyl and hydroxyl additivity parameters in the tropane series (carbonyl α effect -17.2 ppm, equatorial hydroxyl: α +46.8, γ -1.1 ppm, axial hydroxyl: α +47.9, γ -0.9 ppm) differ from those in the analogous piperidine |carbonyl(-14.7 ppm), equatorial hydroxyl α +42.6 and γ -2.7 ppm and axial hydroxyl α +28.1 and γ -4.7 ppm, respectively.|. On the basis of these effects evidence is presented for boat contributions to the conformation of tropine (38).

The intra-molecular hydrogen bonding present in the three tropanes, ecgonine methyl ester (45), 3α-diphenylhydroxymethyl-3β-

tropanyl phenyl ketone (3) suggested by Casy et al.[24] was clarified by comparing the protonation effects observed in the carbon-13 spectra. The conformational change from boat to chair conformers is best exemplified in 47 and 3. The change is calculated by observing shielding at C-6,7 (5.0 ppm) and C-2,4 (7.0 ppm) and deshielding at C-1,5 (2.5 ppm). No effect is observed at the carbonyl carbon. The hydrochloride derivatives of 45 and 49 are also present in boat conformations for solutions in methanol but an equilibrating mixture is observed in less polar media ($CDCl_3$) with the chair conformation predominating. It is suggested that 47 exists preferentially as a boat conformer with a strong nitrogen-carbonyl interaction similar to that found in 3. The hydrochloride, 3a, dissolved in methanol is a ketone/alcohol equilibrium mixture as shown by the carbon-13 spectra. Evidence is presented for a zwitterion in 3α-phenyltropane-3β-carboxylic acid (48).

E. EXPERIMENTAL

Dr. J. E. Coates supplied samples of 36, 43-49 and 3. The hydrochloride of 3α-phenyl-3β-tropanyl phenyl ketone 3 was isolated by bubbling anhydrous HCl into an ether solution of the free base. A white precipitate of mp 254-257° was obtained (mp lit.[11] 257-257.5°).

The free base, 3α-phenyltropane-3β-carboxylic acid (48) was prepared by the addition of a 5% sodium hydroxide solution to 3α-phenyltropane-3β-carboxylic acid·HCl (48a) dissolved in a minimum amount of water, extraction with chloroform, dried over $MgSO_4$ and evaporated to dryness afforded white crystals, mp 121-122° (mp lit.[115] 121-122.5°).

CHAPTER IV

PHOSPHORUS HETEROCYCLES

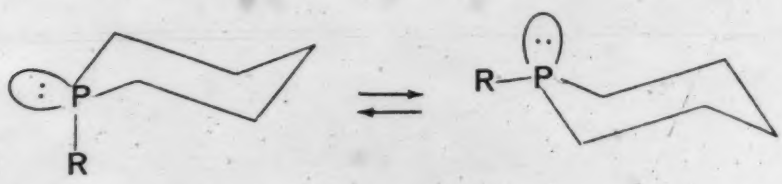
A. INTRODUCTION

Carbon-13 nmr spectroscopy has been employed with much success to six-membered nitrogen heterocyclic compounds. However, until very recently little was known concerning ^{13}C chemical shift parameters in rings containing a phosphorus atom. We attempted to rectify this situation in the present study by relating structural and stereochemical features to carbon-13 chemical shifts and J_{CP} coupling constants. Our work has been complemented by the very recent work of Quin and co-workers[73a,b,74]. These authors have concentrated on the use of ^{13}C nmr spectroscopy to determine the structures of the cis- and trans-isomers of the 1,4-disubstituted-4-phosphorinanols[74], and the chair-to-chair inversion equilibria of selected 1-substituted phosphorinanes and their corresponding sulphides[73a,b]. Our studies have concentrated on the effect of substituents at the C-2,6 and C-3,5 positions on the conformation and chair-to-chair interconversion of 1-phenyl-4-phosphorin -anes, -ones and -ols. The effects of oxide formation were also determined.

Carbon-13 nmr spectra of compounds containing phosphorus exhibit not only characteristic chemical shifts but also coupling between the phosphorus and carbon atoms through two and sometimes three bonds. The size of the two-bond coupling for trivalent phosphorus is apparently subject to steric control and consequently is of value in conformational analysis[74,78]. Further, carbon-13 coupling with

phosphorus exhibits distance[74] and directional[74] characteristics and, therefore, is a useful aid in carbon assignment.

The orientation of the phosphorus substituent is of conformational interest since in the phosphorinane system the ΔH° value is remarkably small for the equilibrium between a and b (-0.68 kcal/mole,



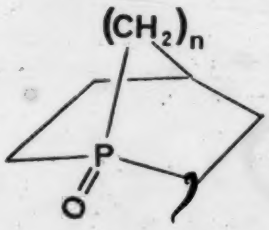
a b

R = CH_3)[73a]. A low-temperature ^{31}P nmr study[116] on 1-methylphosphorinane gave a constant (0.56) for the conformational equilibrium at 25° indicating that the axial form predominates at room temperature. The magnitude of the $^2J_{PC}$ coupling constant to the carbon atoms C-3,5 is apparently specifically related to the position of conformational equilibrium. Large $^2J_{PC}$ values were observed[74] in systems where the dihedral angle between the phosphorus lone-pair orbital and the coupled carbon is small and vice-versa for large dihedral angles. For example, negligible coupling (0-1 Hz) occurs at C-3,5 in trans-1-methyl-4-t-butyl-4-phosphorinanol[74], while significant coupling (7 Hz) occurs in the cis-isomer[74]. $^2J_{PC}$ coupling values between the phosphorus atom and the carbons C-3,5 in the phosphorinanes studied in this work are compared to these limiting values to determine preferences in equilibria.

The present studies on the phosphorinanes indicate a maximum $^2J_{PC}$ value (33 Hz) occurs when the dihedral angle between the phosphorus

lone pair orbital and the carbon two bonds removed is close to 0°. The coupling decreases (11 Hz) at a dihedral angle of about 60° and reduces to zero as the angle approaches 180°. We conclude that a Karplus type relationship probably holds between the dihedral angle and the $^{2}J_{PC}$ coupling constants. However, in the absence of defined dihedral angles the implied relationship must remain qualitative.

A Karplus relationship may hold for the $^{3}J_{PC}$ coupling values. However, in the phosphines the magnitude of this coupling is too small to be of any consequence. On the other hand, $^{3}J_{PC}$ values increase on oxidation and a Karplus type relationship has been suggested[117] based on the bicyclic phosphine oxides 50a and 50b. The



n = 1 (50a):n = 2 (50b)

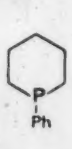
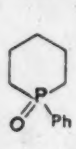
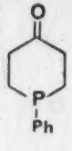
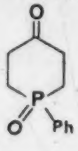
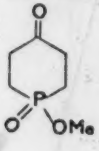
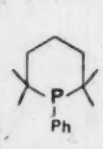
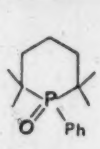
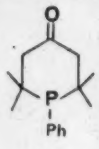
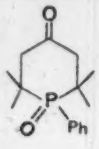
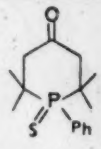
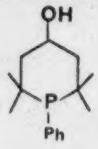
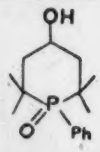
contribution of the dipolar form of the phosphorus-oxygen bond can be estimated from the carbon-13 chemical shifts.

B. RESULTS

The observed ^{13}C chemical shifts for 1-phenyl-, and 1-phenyl-2,2,6,6-tetramethyl- phosphorinanes and their corresponding phosphine oxide derivatives are presented in Table XV. Corresponding J_{CP} coupling constants are given in Table XVI . The effect of changes in the oxidation state (PIII to PIV) are given in Table XVII and the

TABLE XV

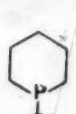
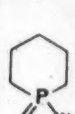
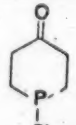
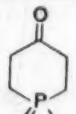
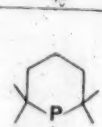
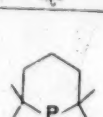
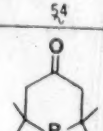
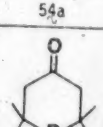
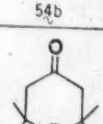
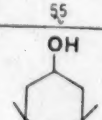
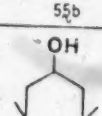
Carbon-13 Chemical Shifts[a] in P-Phenyl-Phosphorinane and Phosphorinane Oxide Derivatives

Carbon Position	Structure 51 	51a 	15 	15a 	52 	53 	53a 	54 	54a 	54b 	55 	55a 
C-2,6	24.7_0	28.4_3	23.7_6	26.9_7	23.7_1	29.2_7	34.4_4	35.1_7	37.9_2	39.7_8	32.1_7	35.0_6
C-2'6'(a)						30.1_0	25.0_6	30.9_9	25.4_1	26.9_2	26.4_9	25.4_9
C-2'6'(eq)						30.6_1	25.0_6	30.1_3	25.4_1	26.9_2	32.3_4	25.5_9
C-3,5	23.5_5	22.0_9	38.2_9	36.2_8	36.8_7	37.6_0	39.2_2	53.0_2	53.6_8	53.9_5	51.1_1	47.3_6
C-4	27.7_8	26.6_5	210.1_2	207.3_1	206.8_8	20.3_4	18.9_6	210.9_1	206.5_3	206.0_5	65.7_6	63.8_9
C-$\underline{q}$	140.8_2	133.6_5	137.4_0	131.3_1	OCH_3 51.0_6	137.4_2	129.1_2	135.8_6	128.1_2	128.2_2	133.3_9	127.5_8
C-$\underline{o}$	130.3_5	130.0_6	130.1_7	130.1_5		136.3_4	132.2_5	135.8_6	132.6_5	133.8_7	137.1_0	133.5_4
C-$\underline{m}$	128.2_3	128.7_0	128.8_8	129.0_4		127.6_1	128.3_6	128.3_7	128.4_9	128.5_8	127.7_2	127.8_8
C-$\underline{p}$	127.1_5	131.6_8	128.0_2	132.4_4		128.8_7	131.5_8	129.7_8	131.9_5	131.8_2	129.5_8	131.5_7

[a] Solvent: $CDCl_3$.

TABLE XVI

^{13}C-^{31}P Nuclear Spin Coupling Constants[a] for P-Phenyl-Phosphorinane and Phosphorinane Oxide Derivatives

Carbon Position	Structure 51	51a	15	15a	52	53	53a	54	54a	54b	55	55b
												
C-2,6	12.2	65.9	15.9	65.9	89.1	12.6	57.4	19.5	61.0	42.7	17.1	61.0
C-2'6'(a)						24.4	37.8	33.0	12.2	24.4	4.9	23.2
C-2'6'(eq)						15.9	37.8	13.4	12.2	24.4	28.1	23.2
C-3,5	3.7	6.1	0	6.1	6.1	0	0	2.4	0	0	11.0	0
C-4	0	0	0	7.3	9.8	0	8.5	0	8.5	6.1	0	6.1
C-q	18.3	89.1	17.1	97.7	OCH_3 6.1[3]	25.6	81.8	23.2	85.2	66.0	26.9	78.1
C-o	14.6	9.8	14.6	8.5		23.1	8.5	23.2	7.3	8.6	23.2	8.5
C-m	4.9	12.2	4.9	12.2		8.5	11.0	9.2	11.0	8.6	8.5	11.0
C-p	0	0	0	0		0	0	0	2.3	3.7	0	2.4

[a] given in Hertz, sign not determined.

TABLE XVII

P-Oxide Substitution Parameters[a] for P-Phenyl-Phosphorinane Derivatives

	Structure													
	51 ⟶ 51a		15 ⟶ 15a		58a[b] ⟶ 58aa		53 ⟶ 53a		54 ⟶ 54a		54 ⟶ 54b		55 ⟶ 55a	
Carbon Position	$\Delta\delta$	ΔJ_{CP}	$\Delta\delta$	ΔJ_{CP}	$\Delta\delta$	ΔJ_{CP}	$\Delta\delta$	ΔJ_{CP}	$\Delta\delta$	ΔJ_{CP}	$\Delta\delta$	ΔJ_{CP}	$\Delta\delta$	ΔJ_{CP}
C-2,6	3.7	53.7	3.2	50.0	3.7	48.8	5.2	44.8	2.8	41.5	4.6	23.2	3.0	46.1
C-2'6'(a)					C-3'5' -0.2	C-3'5' 13.4	-5.1	21.9	-5.6	-1.2	-4.1	11.0	-1.0	18.3
C-2'6'(ee)							5.6	13.4	-4.7	-20.8	-3.2	-8.6	-6.8	-4.9
C-3,5	-1.5	2.4	-2.0	6.1	-1.7	4.9	1.6	0	0.7	2.4	0.9	0	-3.8	-11.0
C-4	-1.1	0	-2.8	7.3	-2.4	4.9	-1.4	8.5	-4.4	8.5	-4.9	6.1	-1.9	6.1
C-*i*	-7.2	70.8	-6.1	80.6	-6.4	84.1	-8.3	56.2	-7.7	62.0	-7.6	42.8	-5.8	51.2
C-*o*	-0.3	-4.8	-0.02	-6.1	[c]	[c]	-4.1	-14.6	-3.2	-15.9	-2.0	-14.6	-3.7	-14.7
C-*m*	0.5	7.3	0.2	7.3			0.8	1.5	0.1	1.8	0.2	-0.6	0.2	2.5
C-*p*	4.5	0	4.4	0			2.7	0	2.2	0	2.0	3.7	2.0	2.6

[a] $\Delta\delta$ given in ppm = $\delta P(O) - \delta P$

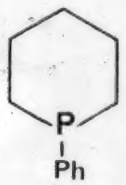
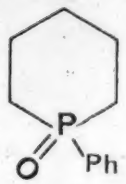
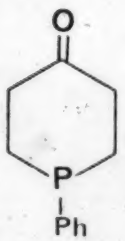
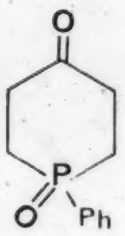
ΔJ_{CP} given in Hertz = $J_{CP}\ P(O) - J_{CP}\ P$

[b] For structure see Table XX.

[c] Not obtainable, see Table XX.

TABLE XVIII

Empirical Tetramethyl Parameters Observed in P-Phenyl-Phosphorinane Derivatives

Structure	Parameters				
	α	β	γ(C-4)	γ(C-q)	δ(C-o)
	+4.6	+14.1	-7.4	-3.4	+5.7
	+6.0	+17.1	-7.7	+4.5	+2.5
	+11.4	+14.8	+0.8	-1.6	+6.0
	+11.0	+17.4	-0.8	-3.2	+2.2

substituent parameters are presented in Table XVIII.

Assignment of the carbon-13 resonances to the appropriate carbon position in the compounds studied was made using conventional techniques and where ambiguities arose, the magnitude of the J_{PC} coupling constants enabled identification. Specific assignments are described in the appropriate section.

C. DISCUSSION

1. Phosphorinane Derivatives

a. 1-Phenylphosphorinane (51) and 1-Phenyl-4-phosphorinanone (15).

The chemical shifts for the title compounds are average values since there exists an equilibrium between P-phenyl (axial) and P-phenyl (equat.). The reported constant for the conformational equilibrium in solution at 27° for 51 is 0.72[73a]. Hence the axial phenyl configuration is preferred at room temperature. However, the conformational preference, in solution, of the phenyl group in 15 has not been reported. As mentioned earlier the magnitude of the coupling constant $^{2}J_{PC}$ between the phosphorus atom and the carbon atoms C-3,5 is related to the position of the conformational equilibrium. Thus, the lack of coupling in 15 indicates the phenyl group prefers an axial orientation, while the value of 3.7 Hz in 51 is in keeping with the conformational equilibrium reported[73a]. The coupling constants to the ortho, meta and para carbons in the phenyl rings of 51 and 15 are identical, 14.6, 4.9 and 0 Hz, respectively, while the C-q coupling is slightly smaller in 15 (17.1 Hz) than 51 (18.3 Hz) suggesting that in the aromatic ring only the $^{1}J_{PC}$ coupling constant is sensitive to small

changes in conformational equilibrium. The ^{13}C evidence suggests the P-phenyl axial configuration in 15 predominates at room temperature and to a lesser extent in 51.

The α-carbonyl substituent parameter in these molecules is +14.7 ppm. This value is identical to that observed in N-methyl piperidines[43]. It is also apparent that the difference in the substituent at the heteroatom has little effect on the overall chemical shifts. For comparison, the ^{13}C resonances for the C-3,5 and C-4 carbons in N-methyl (Table VIII) and N-phenylpiperidine (Figure 12, see page No.131) differ only by +0.2 and -0.5 ppm, respectively. Evidently the carbonyl group has similar inductive effects independent of the heteroatom.

b. 1-Phenyl-2,2,6,6-tetramethylphosphorinanes

Assignment of the carbon-13 resonances to the appropriate carbons in the tetramethylphosphorinanes was made using conventional techniques. In particular the methylene carbons of the saturated ring in 53 were assigned on the basis that C-3,5 will experience a deshielding β-effect and C-4 a shielding γ-effect compared to 51 (β +14.1 ppm, γ -7.4 ppm). For the aromatic carbons in 53, 54 and 55 distant dependent J_{PC} coupling constants were evident. The *para* carbons were identified by their lack of coupling to phosphorus, the *meta* carbons to their insensitivity to substitution effects (chemical shifts remaining constant 127.6 - 128.5 ppm), while the *ortho* carbons were consistently to low field of the other aromatic carbons. In 55 proton selective decoupling techniques were used to confirm their assignments. The assignment of the methyl carbons is described below in relation to the conformation of the compounds.

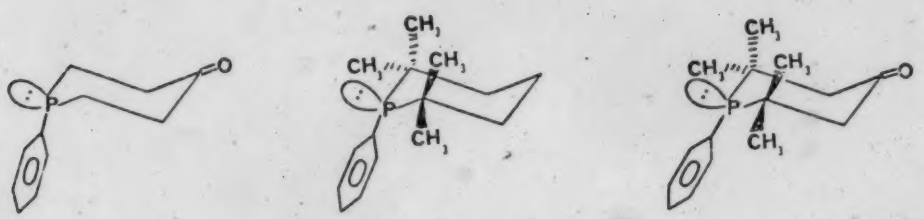
c. Conformational Analysis of 1-Phenyl-2,2,6,6-tetramethyl phosphorinanes.

The conformation of the three tetramethyl-phosphorinanes studied may be analyzed using the observed ^{13}C chemical shifts and the magnitude of the conformationally biased $^{2}J_{PC}$ coupling constant. The methyl carbons in 53 and 54 are almost magnetically equivalent. The difference in chemical shift between the axial and equatorial groups is 0.5 and 0.9 ppm, respectively. However, in 55 there is a definite change either in the ring conformation or the P-phenyl orientations, the methyl resonances differing by 5.8 ppm.

The phosphorinane ring is flattened compared with cyclohexane or other six-membered rings due to the constraints of the phosphorus atom. Thus the deshielding δ-effect expected between the axial methyl carbons may be relieved. A concomitant shielding of the equatorial methyl carbons is likely to arise from partial eclipsing of the $C_2 - C_{me}$ bond with the P - C-q bond, the consequence of distortion of the P-phenyl axial group. The combination of these effects implies that if a conformational equilibrium does exist then the preferred conformation will be that with the pseudo-axial phenyl orientation producing near equivalence of the ring methyl carbons 30.1_0 (ax) 30.6_1 (equat) and 30.9_9 (ax), 30.1_3 (equat) in 53 and 54, respectively. On examining the Dreiding models for these molecules the pseudo-axial methyl groups have a smaller dihedral angle relative to the phosphorus lone-pair orbital (~0°) compared to the pseudo-equatorial groups (>60°). The cis relationship in the former explains the larger coupling constant, 24.4 and 33.0 Hz (compared with 15.9 and 13.4 Hz for the equatorial groups) in 53 and 54, respectively. In 54 phosphorus

coupling to C-3,5 is observed (2.4 Hz) and can be rationalized by a decrease in the dihedral angle between the phosphorus lone-pair orbital and this carbon position. Furthermore, as indicated by Dreiding models this change in angle would cause a decrease in the dihedral angle to the pseudo-axial methyls and an increase to the pseudo-equatorial methyls. This is evidenced by the phosphorus coupling to the axial and equatorial methyls increasing and decreasing, respectively. Hence the phenyl ring is expected to be tilted away from the phosphorinane ring in 54 compared to 53. The pseudo-equatorial methyls in 54 are shielded (30.1_3 ppm) with respect to the pseudo-axial methyls (30.9_9 ppm) due to a greater eclipsing of the C_2 - C_{me} and P - C_q bonds and a greater separation of the 1,3-diaxial methyl groups.

These results suggest that changes in conformation in phosphorinane ring systems can be better followed by changes in the carbon-phosphorus coupling constants. The preferred conformations of 15, 53 and 54 are shown below.



15 53 54

The alcohol derivative 55 (of 54) was obtained by a lithium aluminum hydride reduction. The hydride ion ($H^{\ominus}$) presumably attacks

from the less hindered side (Figure 10a) resulting in an axial hydroxyl group[118] (Figure 10b) which would produce severe 1,3-diaxial interactions with the pseudo-axial C-2'6' methyls in the chair conformation. A more favourable conformer (Figure 10c) with the phenyl group equatorially orientated results from chair-to-chair interconversion. The structure of 55 (Figure 10c) is verified since large $^{2}J_{PC}$ coupling to C-3,5 (11.0 Hz) is observed implying an equatorial phosphorus substituent (vide supra). Further, large differences in the chemical shifts of the methyl groups and their coupling to phosphorus are observed 26.4_9 (4.9 Hz) and 32.3_4 ppm (28.1 Hz). These values characterize the axial and equatorial methyl groups, respectively. Examination of Dreiding models indicates that the phosphorus lone pair orbital and axial methyl carbons are trans to each other with a dihedral angle close to 180°, while a cis-relationship is evident in the case of the equatorial methyls. The fact that the couplings to the C-3,5 and C-2',6' (equat) carbons are different (11.0 and 28.1 Hz, respectively) indicates that the dihedral angle is smaller between the phosphorus lone pair and the C-2'6' equatorial methyl groups presumably the consequence of the phenyl group tilting towards the axial orientation.

As the phenyl group becomes progressively more equatorial in 53, 54 to 55 the C-q carbon resonance moves to higher field, 137.4_2 135.8_6 and 133.3_9 ppm, respectively. The possibility that the differing orientations of the methyl groups contribute to increased steric effects at the C-q carbon cannot be ruled out. However, similar shielding was observed in the equatorial phenyl isomer of 1-phenyl-3,5-dimethyl-4-phosphorinanone (vide-infra).

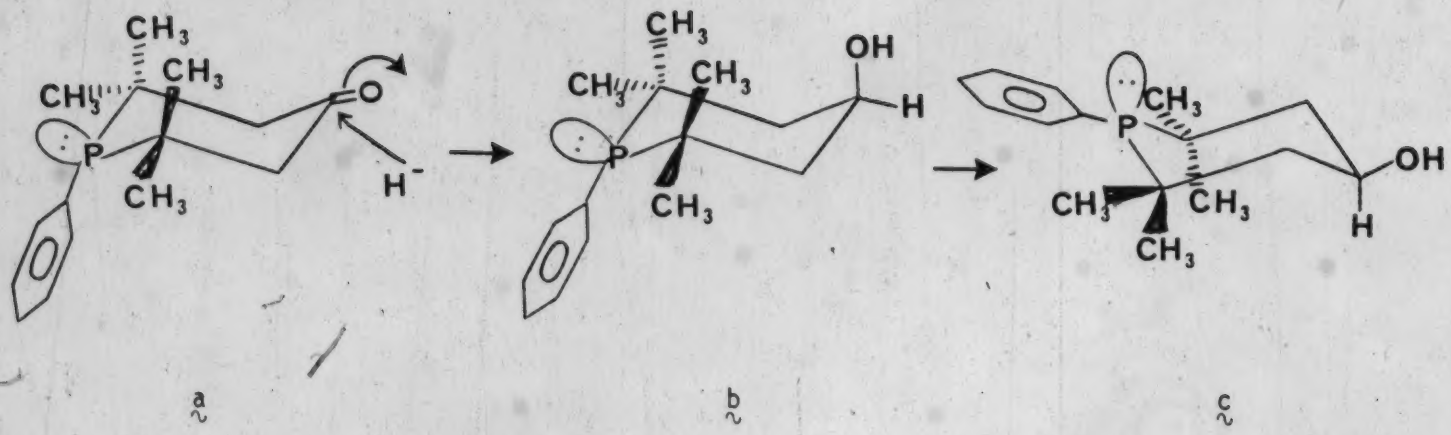
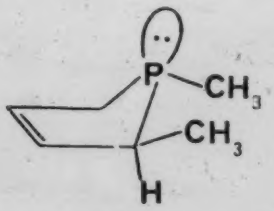


FIGURE 10: Lithium aluminum hyrdride reduction of 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanone.

Consideration of the $^2J_{PC}$ coupling values in 53, 54 and 55 together with those in cis- and trans-1-methyl-4-t-butyl-4-phosphorinanol[74] suggests that the $^2J_{PC}$ coupling has a maximum value (~33 Hz) when the dihedral angle approaches 0° (53) and decreases to about 7 Hz at 60° (cis-1,4-disubstituted phosphorinanol) and to 0 Hz at 180° (15, 53 and trans-1,4-di-substituted phosphorinanol). A graph of these results is presented in Figure 11. Further examples of an approximate 0° dihedral angle corresponding to a $^2J_{PC}$ coupling of 33 Hz have been reported in the literature[79]. The trans-isomers of 1,2-dimethyl-Δ^3-phospholene (56) and 2,5-dimethyl-1-phenyl-Δ^3-phospholene (57) have $^2J_{PC}$ coupling constants to the ring methyls of 32 and 30 Hz, respectively.



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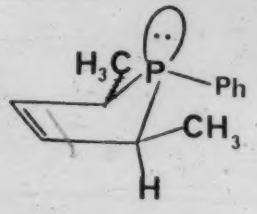

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d. ^1H Chemical Shift and J_{PH} Coupling

The pmr results for the 1-phenyl-2,2,6,6-tetramethyl-phosphorinanes are presented in Table XIX. The axial methyls are assigned to the low field resonance to provide consistency with the proton-selective decoupling experiments for 55. I.e. irradiation of the low field methyl proton resonance (1.2$_8$ ppm) produced enhancement of the carbon resonance at high field assigned to the axial methyl carbon on the basis of the γ-effect experienced at this site. The proton data show the pseudo-axial methyl proton chemical shifts remain constant while the equatorial methyl proton shifts move progressively

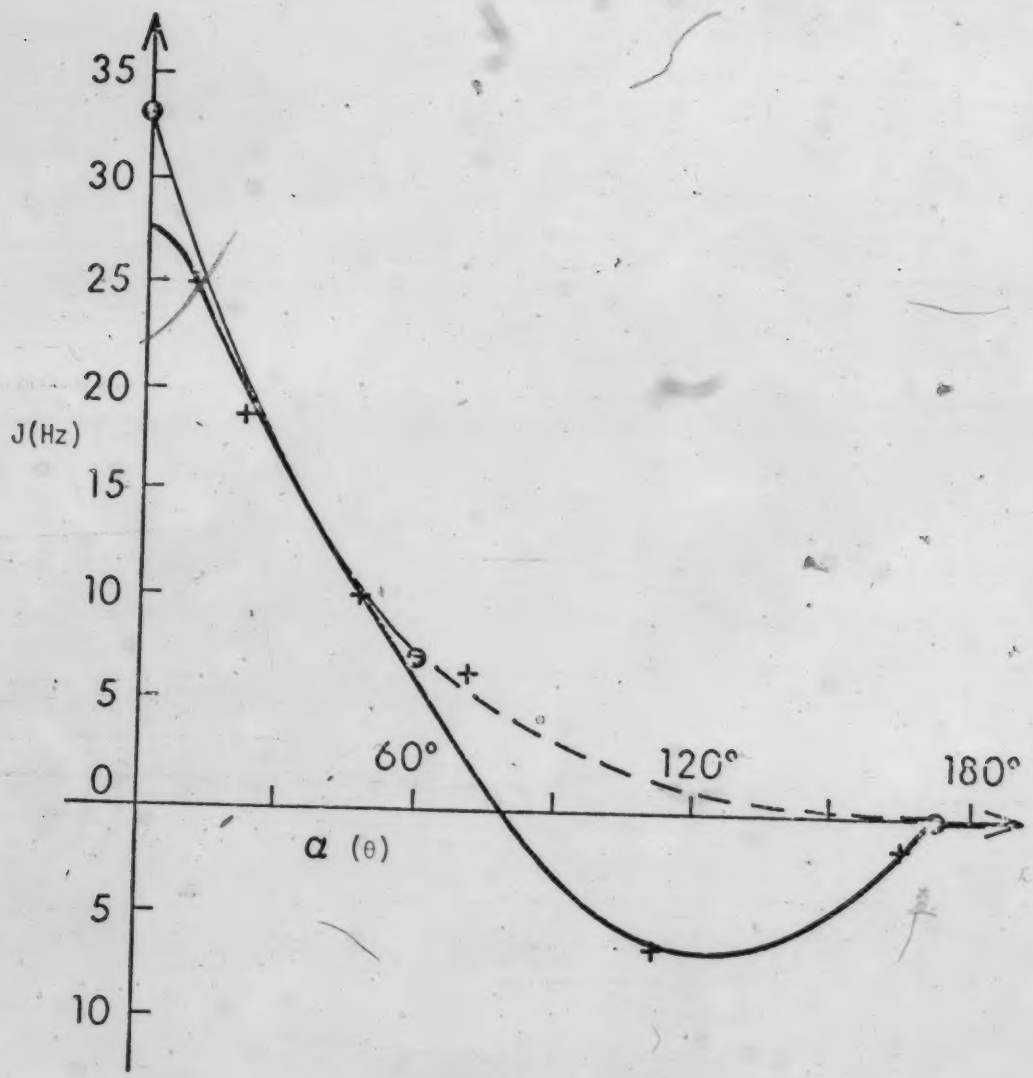


FIGURE 11: A Karplus relationship between the $^{2}J_{PH}$ coupling constant and dihedral angle (θ) (——)[63b] and the $^{2}J_{PC}$ coupling constant and dihedral angle (— , - - -). Since the sign of the coupling constants was not determined the position of the dotted line could indicate positive or negative coupling values.

TABLE XIX

$^{3}J_{P-H}$ Coupling Constants[a], Proton Chemical Shift[b] and Shift Differences[c] for the Methyl Protons in 2,2,6,6-Tetramethylphosphorinane, Phosphine and Phosphine Oxide Derivatives

Compound	C-2'6' axial Me	C-2'6' equatorial Me
53	1.2_8 (19)	0.8_1 (10)
54	1.3_1 (18)	0.9_5 (11)
55	1.2_8 (8)	1.0_8 (23)
53a	1.3_0 (12.5)	1.0_1 (14)
54a	1.3_5 (5)	1.1_3 (6.5)
55a	1.5_0 (12)	1.1_2 (12)
53a	$+0.0_2$[c]	$+0.2_0$[c]
54a	$+0.0_4$	$+0.1_8$
55a	$+0.2_2$	$+0.0_4$

[a] Values in parenthesis given in Hertz. Signs not determined.

[b] Given in ppm downfield from TMS, solvent $CDCl_3$.

[c] Given in ppm, plus indicates oxide derivative to low field.

($\underset{\sim}{53} \rightarrow \underset{\sim}{55}$) to lower field with a concomitant increase in the $^{3}J_{PH}$ coupling constant. This is expected since any change in the orientation of the phenyl group towards equatorial will affect the equatorial methyl group, the methyl protons being in the deshielding zone of the phenyl ring. The magnitude of the $^{3}J_{PH}$ coupling is known to have a geometrical dependence[119] similar to that described for the $^{2}J_{PC}$ values. Thus, the increase in $^{3}J_{PH}$ couplings is consistant with the changes in phenyl group orientation previously suggested. The larger coupling (19 Hz) to the low field C-2'6' methyl protons in $\underset{\sim}{53}$ and $\underset{\sim}{54}$ compared to the high field methyl protons (11 Hz) substantiates the assignment to the pseudo-axial and equatorial methyl groups, respectively. The phenyl group is in the axial orientation. Analogous values are reported[119] for the $^{3}J_{PH}$ couplings to the C-2' methyl protons in the cis- and trans-isomers of $\underset{\sim}{56}$ (P-CH_3 or P-Ph) 10 Hz and 18 Hz, respectively, indicating similar geometric relationship between the methyl groups and phosphorus lone pair orbital in these isomers.

In $\underset{\sim}{53}$ and $\underset{\sim}{54}$ the methyl proton chemical shifts and $^{3}J_{PH}$ coupling constants are less sensitive to the conformational change than the analogous carbon-13 data. However, the change to a chair conformation with an equatorial phenyl group as in $\underset{\sim}{55}$ is also indicated by the proton data. The axial methyl protons at 1.2_8 ppm have a small $^{3}J_{PH}$ coupling constant of 8 Hz, while the equatorial methyl protons resonate at lower field (1.0_8 ppm) with a significantly larger coupling (23 Hz). These results are consistant with the size of the dihedral angle between the phosphorus lone pair orbital and the respective methyl group. In $\underset{\sim}{53}$ and $\underset{\sim}{54}$ the corresponding couplings to the equatorial methyl protons are 10 and 11 Hz, respectively.

e. ^{13}C Additivity Relationships

Due to a difference in the conformations of the three tetramethylphosphorinanes 53, 54 and 55 discussion of additivity effects of the carbonyl and hydroxyl group is not valid. However, the effects of tetramethyl substitution in the phosphorinanes 51 and 15 can be discussed.

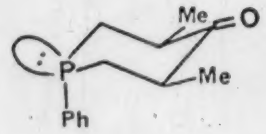
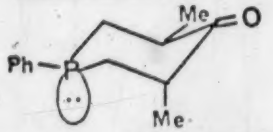
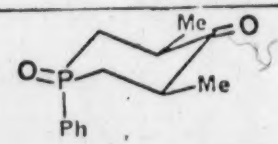
The shifts induced at C-3,5 (β-effect) on substitution of the geminal methyl groups at C-2 and C-6 are similar, +14.1 and +14.8 in 53 and 54, respectively. The α-effect is attenuated in 51 (+4.6 ppm) and 15 (+11.4 ppm) confirming the suggestion that a conformational difference exists between these molecules. A γ-gauche shielding effect is observed at C-4 (-7.4 ppm) in 51, while in 15 the removal of the C-4 proton greatly attenuates this effect (+0.8 ppm). A γ-effect is also observed at C-q in the phenyl group, the largest effect being in 51 (-3.4 ppm). A large δ-deshielding effect is found at the ortho carbons (+5.7 and +6.0 ppm in 51 and 15, respectively) and probably arises from sym-axial interactions. These data are summarized in Table XVIII.

f. 1-Phenyl-3,5-dimethyl-4-phosphorinanone (58)

Evidence for three major isomeric products of 1-phenyl-3,5-dimethyl-4-phosphorinanone (58) in the crude reaction product arising from the condensation of phenylphosphine and 2,4-dimethyl-1,4-pentadien-3-one was indicated by the observation of three carbonyl resonances at 212.3, 213.2 and 214.5 ppm in the carbon-13 nmr spectrum. The carbon-13 chemical shifts for the three isomers and the major phosphine oxide derivative are presented in Table XX. The presence of three isomers was also indicated in the pmr spectrum which exhibited

TABLE XX

Carbon-13 Chemical Shifts[a] of 1-Phenyl-3,5-Dimethyl-4-Phosphorinanone Isomers and Major P-oxide Isomer

	Structure	Carbon Position									
		C2	C3	C4	C5	C6	C3'	C5'	C-q		
58α		34.0_1	41.9_2	213.2_5	41.9_2	34.0_1	16.7_8	16.7_8	137.6[b]		
		15.9	0	0	0	15.9	0	0	16.0		
58β		36.1_7	43.2_4	212.2_8	43.2_4	36.1_7	17.4_8	17.4_8	131.8[b]		
		11.0	8.6	0	8.6	11.0	0	0	21.9		
58γ		29.0	41.4	214.3	39.0	29.6	16.6	18.0	- [d]		
		15.9	10.9	0	4.9	13.4	0	0	-		
									C-c	C-m	C-p
58αa		37.6_8	40.1_9	210.8_2	40.1_9	37.6_8	16.5_9	16.5_9	131.2_5	130.2_8	128.8_8	132.2_8
		64.7	4.9	4.9	4.9	64.7	13.4	13.4	100.1	9.8	12.2	0[c]

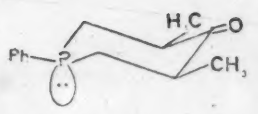
[a] Solvent $CDCl_3$.

[b] Only C-q chemical shifts obtainable due to overlapped of o, m and p resonances.

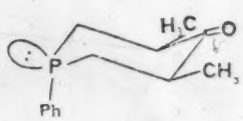
[c] Broad resonance.

[d] Concentration of isomer too small to obtain chemical shift.

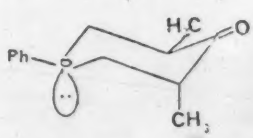
five methyl resonances having similar chemical shifts and coupling constants to those reported by Katritsky and co-workers[120] for the product obtained from cyclization of bis-(2-methoxycarbonylpropyl)-phenylphosphine in their attempts to prepare the title compound 58, i.e., 0.9_8 (6.4 Hz), 1.0_8 (6.5 Hz) and 1.2_4 ppm. The doublets were assigned to the major isomers 58β and 58α, respectively, and the resonance at 1.2_4 ppm to the trans-isomer 58γ. Other methyl resonances were obscured.



58β



58α



58γ

Column chromatography on alumina separated the isomers 58α and 58β from 58γ. Furthermore, the relative concentrations of the isomers 58α and 58β differed before and after chromatography. The isomer, 58β predominated in the original mixture while the isomer, 58α dominated after chromatography. Further separation could not be achieved using these techniques. The mixtures were, therefore, studied and carbon-13 nmr data was abstracted by difference measurements.

The absence of phosphorus coupling to the carbons C-3,5 in 58α identifies the axial orientation of the phenyl group. In contrast, the $^2J_{PC}$ coupling constant 8.6 Hz is observed in 58β characterizing the equatorial orientation of the phenyl group. A steric γ-effect of -1.4

ppm is observed at C-3,5 in 58α. Comparison of the data for 58α and 15 enables derivation of the equatorial methyl parameters (α, +3.7 and β, +10.2 ppm) which are 1 ppm greater than those in the analogous N-methylpiperidine. (Chapter II, Table II, α +2.8 and β +9.1 ppm). Comparison of 58β and 58α now enables the derivation of the parameters for the change in orientation of the phenyl group. These values are α, -2.2; β, -1.3 and γ, +0.9 ppm. The C-q carbon shift (137.6 ppm) in 58α is identical to that in 15. In 58β where the phenyl group is established as equatorial the C-q chemical shift is to high field (131.8 ppm). This upfield shift is the reverse of that observed in the axial compared to equatorial orientated 4-phenyl substituent in nitrogen heterocycles[55,56]. However, the concomitant shift at C-3,5 for this change in orientation (-1.3 ppm) was observed. It seems probable that the P-Ph bond contributes to the reversed effect.

The absence of symmetry in the isomer, 58γ, is shown by the presence of distinct resonances for each ring carbon atom. The β-effect of an axial compared to an equatorial methyl suggests that C-2 (29.0 ppm) should be to high field of C-6 (29.6 ppm). The expected γ-effect of the C-3' methyl group at C-5 suggests the resonance at 39.0 ppm be assigned to C-5 and that at 41.4 ppm to C-3. The equatorial methyl group C-5' (18.0 ppm) was assigned by comparison with the similar methyl in 58β (17.5 ppm). The axial methyl group C-3' is thus to high field (16.6 ppm).

The phosphorus coupling to the carbons C-2,6 is larger in 58α than 58β (15.9 and 11.0 Hz, respectively) a feature also observed in 1-methyl-4-phosphorinanols[74] where $^{1}J_{PC}$ coupling is larger when the P-substituent is axial. However, an opposite result is obtained for the

coupling to C-q, while the methyl in the phosphorinanols has a larger coupling when axially oriented. It is clear that discussion relating steric effects and $^{1}J_{PC}$ couplings must consider similarly hybridized carbon atoms. In our case the axially oriented sp^2 hybridized benzene carbon induces smaller couplings than a corresponding sp^3-methyl carbon.

2. Phosphorinane Oxide Derivatives

The carbon resonances of the phosphorinane oxides were assigned using conventional techniques, in particular, proton selective decoupling. For 1-methoxy-1-phenyl-4-phosphorinanone 52, C-2,6 was distinguished from C-3,5 by its larger J_{PC} coupling constant. Significant changes accompany conversion to the oxide: 1) the oxygen atom exerts characteristic α-, β- and γ-effects, 2) the electron density on phosphorus is diminshed compared with the phosphine, 3) changes in bond angle and bond lengths occur, and 4) anisotropic effects may differ between phosphines and their oxides. The carbon-13 chemical shift of the oxides are presented in Table XV and the corresponding J_{PC} coupling constants in Table XVI.

a. (i) Conformational and Additivity Effects

It is known that peroxide oxidation of phosphines is accompanied by retention of configuration[121]. Hence the basic conformations of the cyclic phosphines established earlier should be retained.

The average β-effect of the oxygen at C-2,6 in 51a, 15a and 58αa compared to their corresponding phosphines is +3.5 ppm, while in the tetramethyl derivatives the effect varies with conformation from

+2.8 ppm in 54a to +5.2 ppm in 51a. In 55a the β-effect is +3.0 ppm. It is noteworthy that while the β-effect at C-2,6 is deshielding, a large shielding effect occurs at the corresponding site, C-q (-5.8 → -8.3 ppm). An explanation follows (section b). Of greater significance is the γ-effect of the oxygen which is expected to be similar to that in sulphide derivatives[73]. Shielding effects (-1.5, -2.0 and -1.7 ppm) are observed at C-3,5 in 51a, 15a and 58αa, respectively, which correspond with similar effects reported for the 1-methyl and 1-phenylphosphorinane sulphides[73a], -1.0 and -1.6 ppm, respectively. This shielding was taken as evidence for the sulphur atom being largely in an axial orientation[73]. However, this is probably not the case in the oxides. We have observed that in both phosphine oxide isomers of 8-phenyl-8-oxo-8-phosphobicyclo-|3.2.1.|octan-3-one the γ-effect is shielding (vide-infra). Further the corresponding chair conformer of 58αa with an axial oxygen atom is unlikely to contribute due to severe 1,3-diaxial interactions. The aromatic carbon atoms shifts in 58αa and 15a are also identical which suggest that the same conformation holds for both molecules. It appears, that in the phosphorinanes, the γ-effect due to phosphine oxide oxygen is upfield in both axial and equatorial orientations of the oxygen with the larger effect in the former.

Consideration of the chemical shifts of 15a and 52, in particular, the similar shielding at C-3,5, 36.2_8 and 36.8_7 ppm, suggests similar conformations for these compounds. The shielding effect (-3.3 ppm) at C-2,6 in these systems is indicative of the difference in the inductive effects of the phenyl and methoxy groups.

The conformation of the tetramethyl phosphine oxide derivatives should be approximately the same as the parent phosphine. The axial

oxygen atom in 55a does cause the expected γ-shielding effects at C-3,5 (-3.8 ppm), at C-o (-3.7 ppm) and C-2',6' (equat) (-6.8 ppm) (Table XVII). The latter data reinforces the assignment of these carbon atoms since the C-2',6' (axial) methyl groups are only slightly shielded (-1.0 ppm) relative to those in the phosphine and the meta carbons are not affected (+0.2 ppm) on oxidation.

The carbon and proton chemical shifts are consistent. On oxidation the methyl proton resonances are deshielded (Table XIX) while the carbon resonances are shielded (Table XVII). In particular in 55a the equatorial methyl carbon is shielded (-6.8 ppm) to a larger extent than the axial (-1.0 ppm) while the proton shift differences (Table XIX) are $+0.2_2$ and $+0.0_4$ ppm, respectively.

The β-oxygen substitution effects in 53a and 54a (-8.3 and -7.7 ppm, respectively) are different than in 55a (-5.8 ppm). This is probably due to the change in phenyl group conformation, from pseudo-axial in the former to equatorial in the latter. The γ-oxidation effect on the C-2,6' methyl carbons (axial and equatorial) are approximately the same in 53a (-5.1 and -5.6 ppm, respectively) suggesting a similar orientation of these methyl groups about the phosphine oxide bond. While in 54a and effect differs, (-5.6 and -4.7 ppm, for axial and equatorial methyls, respectively). This is consistent with the change in orientation of the phenyl group in going from 53a to 54a. In the latter, the greater γ-effect on the axial methyl compared to the equatorial is attributable to further eclipsing of the P-O and $C\text{-}Me_{(ax)}$ bonds than the P-O and $C\text{-}Me_{(equat)}$ bonds.

Oxidation of tetramethylphosphorinanes gives a shielding δ-effect at C-4 (-1.4, -4.4 and -1.9 ppm for 53a, 54a and 55a,

respectively). The increase in value is associated with the presence of the carbonyl group. A similar observation was made for the less substituted derivatives (-1.1, -2.8 and -2.4 ppm in 51a, 15a and 58αa, respectively). Generation of the sulphide (54b) gives similar shielding parameters to those in the oxide (54a) (Table XVII), with the exception of the β-effect, which is larger in the sulphide (+4.6 ppm).

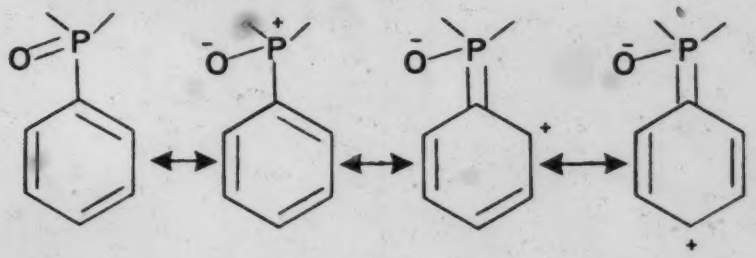
a. (ii) P-atom Hybridization

Changes in the oxidation state of phosphorus from PIII to PIV, result in rehybridization of the atomic orbitals of phosphorus. The amount of s-character is increased in PIV compounds and hence a large increase is observed in the $^{1}J_{PC}$ coupling constants (50 Hz in the molecules studied). Of particular interest is the long range $^{3}J_{PC}$ coupling constant which is larger than $^{2}J_{PC}$ in both the saturated and aromatic rings. A similar observation was made in the triphenylphosphorus ylides[122] although no explanation was offered. The long range coupling constants were used to confirm the aromatic ring carbon atom assignments ($^{3}J_{PCm} > {}^{2}J_{PCo}$)

b. The Phosphorus-Oxygen Bond

The amount of π-bonding in the P-O bond of phosphine oxides is of theoretical interest and has been the source of much controversy[82,123,124]. Comparison of the ^{13}C chemical shifts of the C-p carbon in the phosphine and phosphine oxides in the series of compounds studied (Table XVII) reveals a large deshielding effect on formation of the oxide. Values range from +4.4 ppm in 51 and 15 to +2.0 ppm in tetramethyl derivatives. These large shift differences

(an ε-effect) are not attributable to an inductive effect but rather a resonance effect. Delocalization of the aromatic π-electrons towards phosphorus, decreases the electron density at C-p, therefore deshielding this position. The results imply the P-O bond is polarized $\overset{\oplus}{P}\text{-}\overset{\ominus}{O}$ and present to a significant amount. The resonance forms possible are:



A similar deshielding effect is not observed at C-o since upon oxidation there is a concomitant large shielding γ-effect at this position. A similar ε-deshielding effect (+2.0 ppm) is also present in the sulphide derivative 54b and one must conclude that the P-S bond is also polarized. In more polar solvents the contribution of the polar form is expected to be enhanced.

Another phenomenon resulting from oxide formation is the large shielding effect on the quaternary carbon, C-q (average -7.1 ppm, not including 55a). This observation presumably arises from electronegativity differences between the carbon and phosphorus atoms, the phosphine oxide bond inducing a build-up of electron density on the quaternary carbon centre.

3. Mono-, Di-, and Triphenylphosphine and their Oxides

While several authors have reported the ^{13}C chemical shifts and coupling constants for triphenylphosphine[71,76,77,125], similar results for the other aryl phosphines and their oxides have not been

previously reported. In order to generalize on the observations concerning oxidation of phosphorus discussed above we have studied the carbon-13 spectra of the series, phenyl, diphenyl and triphenylphosphine and their corresponding oxides. The data is presented in Table XXI.

The assignment of the carbon resonances to the appropriate position was aided by comparison with the chemical shifts in the phosphorinanes. Modulated off-resonance spectra identified the quaternary carbons and the distant dependant J_{PC} coupling constants was used to differentiate the C-o and C-m carbons in the phosphine and phosphine oxide.

The chemical shifts of the phosphines were determined in both $CDCl_3$ and $MeOH_{d-4}$. In these solvents the carbons, C-o, C-m and C-p undergo only minor solvent shifts while the C-q carbon shifts to lower field with increase in phenyl substitution. That is, the β-effect is attenuated. For example, from +6.6 ppm in diphenylphosphine to +1.7 ppm in triphenylphosphine. The absence of change in the chemical shifts of the ortho-, meta- and para-carbons indicates that there is no change in involvement of the phosphorus lone-pair orbital in delocalization into the aromatic ring. It is generally accepted that the electron donating character of the phosphorus atom in arylphosphines is very weak[123]. However on oxidation the increased positive character of the phosphorus atom should confer on itself a higher electron withdrawing character. The ^{13}C chemical shifts of the C-p carbons do indeed exhibit a larger deshielding effect (+4.6 ppm) indicative of the resonance effects discussed earlier. The ortho position is shielded (γ-effect) with the shift to high field becoming greater in the less substituted phosphine. Oxidation of triphenylphosphine (59) exhibits a

TABLE XXI

^{13}C Chemical Shift[a], J_{PC} Coupling Constants[b] and Oxide Additivity Parameters[c] in Mono-, Di- and Triphenyl-phosphine and their Oxides

	^{13}C-Chemical Shifts[a] Structure									
	59	59	60	60	61	61	59a	60a	61a	61a
Carbon Position	ϕ_3P^{Δ}	$\phi_3P^{\square}$	ϕ_2PH^{Δ}	$\phi_2PH^{\square}$	ϕPH_2^{Δ}	$\phi PH_2^{\square}$	$\phi_3P(O)^{\Delta}$	$\phi_2P(O)H^{\Delta}$	$\phi P(O)H_2^{\Delta}$	$\phi P(O)H_2^{\Delta}$
C-q	137.3_5	139.0	134.6_2	135.4_3	128.0_1	128.9_8	132.3_0	134.5_1	128.2_0	130.5_8
C-o	133.7_9	134.7_3	133.9_2	134.4_3	134.5_7	135.4_3	132.6_5	132.2_4	130.7_7	134.2_7
C-m	128.5_0	129.6_3	128.4_7	129.0_9	128.0_1	128.9_8	129.6_3	129.6_3	128.6_3	131.5_9
C-p	128.6_6	129.8_5	128.3_4	128.9_3	128.3_9	129.3_6	133.3_0	133.1_9	132.8_1	130.3_2
	J_{PC} Coupling Constants[b]									
C-q	12.2	25.6	15.9	11.0	4.9	4.9	108.6	137.9	15.9	47.6
C-o	19.5	20.8	15.9	17.0	15.9	15.9	9.8	11.0	12.2	17.1
C-m	7.3	9.8	6.1	7.3	4.9	4.9	12.2	12.2	13.4	22.0
C-p	0	0	0	0	0	0	0	broad	2.4	6.1

TABLE XXI (cont'd)

^{13}C Chemical Shift,[a] J_{PC} Coupling Constants[b] and Oxide Additivity Parameters[c] in Mono-, Di- and Triphenylphosphine and their Oxides

	Oxide Additivity Parameters[c]			
	ϕ_3P	ϕ_2PH	$\phi PH_2(CDCl_3)$	$\phi PH_2(MeOH_{d-4})$
C-q	-5.0	-0.1	+0.2	+1.6
C-o	-1.2	-1.7	-3.8	-1.2
C-m	+1.1	+1.2	+0.6	+2.6
C-p	+4.6	+4.8	+4.4	+1.0

[a] Solvent $CDCl_3$ $^{\Delta}$, $MeOH_{d-4}$ $^{\square}$, $\phi_3P(O)$ and $\phi_2P(O)H$ insoluble in MeOH.

[b] Given in Hertz, signs not determined.

[c] Given in ppm, negative sign indicates oxide to high field.

shielding effect (-5.0 ppm) at C-q similar in magnitude to that in the phosphorinanes but oxidation of 60 and 61 causes practically no change in the chemical shift of the quaternary carbon. This attenuated effect in the latter may be attributed to an increase in the deshielding β-effect at C-q compensating for any shielding effects imparted by the phosphine oxide bond.

A solvent effect is apparent in the phosphine chemical shifts. The carbon chemical shifts move to lower field in methanol as a consequence of hydrogen bonding of the phosphorus lone-pair with the solvent. This is more noticeable in phenylphosphine oxide (61a). The resonance effect is attenuated as exhibited by the C-p carbon being deshielded (+1.0 ppm) compared to +4.4 ppm in deuterochloroform. The difference in the oxide additivity parameters determined for solutions in $CDCl_3$ and CD_3OD is possibly due to the latter solvent enhancing the dipolar form of the phosphorus-oxygen bond by hydrogen bonding to the P and O atoms. No structural changes were produced by the methanol$_{d-4}$. On changing the solvent back to deuterochloroform the original spectrum was obtained. All other oxides are insoluble in methanol.

The cmr results thus provide evidence of the lack of phosphorus lone-pair electron involvement in delocalization in the phenylphosphines and a significant electron withdrawal effect in the corresponding oxides. The dipolar form of the phosphorus-oxygen bond is enhanced in protic solvents.

4. The 8-Phosphabicyclo[3.2.1.]octan-3-one System

The ^{13}C chemical shifts and coupling constants for the parent compound 62, its methiodide derivative 63, and the two oxide isomers

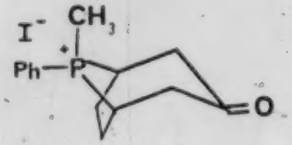
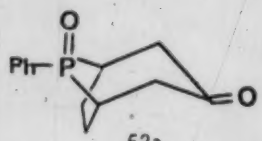
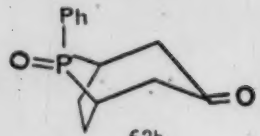
62a and 62b are given in Table XXII. The carbon resonances were assigned by use of conventional techniques, in particular, in 62, C-6,7 was distinguished from C-2,4 by proton selective-decoupling, in 63 by a typical γ-effect at C-2,4 and in 62a and 62b by comparison of the axial and equatorial oxide γ-effects discussed earlier. C-q in 62, 62a and 62b was identified from modulated off-resonance experiments.

The configuration, 62, of the major isomer of 8-phosphabicyclo[3.2.1]octan-3-one has been proved by earlier pmr studies[126]. The equatorial phenyl C-q carbon in 62 exhibits an identical chemical shift to that in 58B (131.8 ppm), indicating that no significant γ-effect is induced by the ethylene bridge. This is somewhat surprising since in the analogous N-methyl tropanone (34) the N-methyl carbon is shielded (-6.8 ppm) compared to N-methyl-4-piperidone[43]. This anomaly suggests that the phenyl orientation may be incorrectly assigned or that the model is bad. This feature can be investigated further by analyzing the $^2J_{PC}$ couplings. Thus the larger $^2J_{PC}$ coupling constant at C-2,4 (14.6 Hz) compared to C-6,7 (4.9 Hz) confirms the cis-relationship between the phosphorus lone-pair and the carbons C-2,4. The phenyl group, therefore, must be equatorially oriented and consequently no significant γ-effect is induced by the ethylene bridge in these compounds.

Changes in the phosphorus atom hybridization are reflected in the $^1J_{PC}$ coupling constants in the phosphonium salt 63, compared to 62. $^1J_{PC}$, is enhanced by 39 Hz at C-1,5 and by 63 Hz at C-q. The β-effects of the methyl group are shielding at C-q (-11.5 ppm) and at C-1,5 (-4.9 ppm), while in the analogous N-methyl derivative the effects are -7.5 ppm and +4.9 ppm, respectively (Chapter III, Table XII, 34,

TABLE XXII

^{13}C Chemical Shifts and J_{P-C} Coupling[a] Constant of 8-phosphabicyclo[3.2.1.]octan-3-one Derivatives

	Structure				
	62	 63		 62a	 62b
Carbon Position	$CDCl_3$	$DMSO_{d6}$[b]	D_2O[c]	$CDCl_3$	$CDCl_3$
C-1,5	36.3_9 (11.0)	31.4_6 (48.8)	29.9_5 (50.0)	30.1_0 (65.9)	31.9_3 (65.9)
C-2,4	49.2_0 (14.6)	46.0_3 (broad)	44.6_8 (4.9)	44.9_1 (6.1)	47.4_2 (0)
C-3	210.6_7 (0)	205.8_6 (3.7)	208.9_1 (6.1)	208.0_0 (7)	206.5_9 (9)
C-6,7	29.6_7 (4.9)	26.8_5 ($8._6$)	25.5_5 (8.6)	23.2_8 (13.4)	25.9_5 (7.3)
P-CH_3		6.2_1 (44.0)	4.8_7 (45.2)		
C-q	131.9_3 (18.3)	120.2_8 (81.8)	116.4_3 (81.8)	130.7_2 (42.7)	131.2_0 (61.0)
C-o	d	133.6_1 (8.5)	131.6_3 (9.7)	d	d
C-m	d	131.4_2 (12.2)	130.5_0 (12.2)	d	d
C-p	d	136.0_6 (0)	135.6_6 (0)	d	d

[a] Given in Hertz shown in parentheses, sign not determined.

[b] Converted to TMS scale using: $\delta_c^{DMSO_{d6}} = 41.17$ ppm.

[c] Converted to TMS scale using: $\delta_c^{Dioxane} = 66.74$ ppm.

[d] Not obtainable due to overlapping of resonances.

34b). At the present time no explanation for the shielding effect at C-1,5 in 63 can be given.

Isolation of the oxide isomers 62a and 62b was not possible. Therefore, the chemical shifts were obtained from mixtures by comparing the relative intensities of the resonances, and by the use of additivity effects. As already mentioned an axial oxygen has a larger γ-effect than an equatorial one. Hence, C-2,4 in 62a is expected to be at high field compared to 62b, i.e., 44.9_1 ppm in 62a, 47.4_2 ppm in 62b. A shielding β-effect (-6.3 ppm) at C-1,5 of an axial oxygen in 62a compared to 62 is observed and differs from the deshielding (+3.0 ppm) found in 55a compared to 55 (Table XVII) where the oxygen is also axial.

The cmr results confirm the conformation of 62 to be a chair with the phenyl group equatorial, in agreement with the pmr data[121]. In the bicyclic system (62) introduction of a substituent at the phosphorus atom causes a shielding effect at C-1,5 in 63 and 62a as opposed to the deshielding β-effect in the tropanes (Chapter III) and 1-oxo-1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanol 55a.

5. Phosphorus, Nitrogen and Carbon Comparisons

As indicated in the above discussion, many phosphorus heterocyclic compounds are characterized by the preference for the substituent on the phosphorus atom to take up the axial configuration unless other driving forces - steric strain, hydrogen bonding, etc., enhance a change in conformation. This feature contrasts the phosphorus systems from analogous carbon and nitrogen compounds in which substituents prefer the equatorial configuration. However, application of the parameters

obtained earlier, for changing the phenyl group from an axial to equatorial orientation, to 51 and 15 enables estimation of the carbon chemical shifts for molecules with an equatorial phenyl group. The resulting chemical shifts are shown in Figure 12.

It is valuable to consider Pauling's electronegativity values for P(2.1), C(2.5) and N(3.0) in relation to the observed chemical shifts. Introduction of an electropositive phosphorus atom in place of carbon appreciably changes the local charge density on the adjacent carbon atoms. The consequent shielding is apparent from the upfield shift (-7.7 ppm) at C-2,6 in 51 (equat. Ph) compared to phenyl cyclohexanone. The effect is attenuated at C-3,5 (-2.2 ppm) and C-4 (+0.9 ppm). The analogous effects between the phosphorus and nitrogen heteroatoms are C-2,6 (-23.8 ppm), C-3,5 (-1.0 ppm) and C-4 (+2.5 ppm). Applying the additivity parameters for changing the nitrogen substituent from methyl to phenyl in the corresponding piperidines (β -6.0, γ -0.2, δ +0.5 ppm - Figure 12 and Table VII) to N-methyl-4-piperidone and 1,3,5-trimethyl-4-piperidone enables a comparison to be made with the analogous phosphorus compounds. (Chemical shifts of the N-phenylpiperidines are given in Figure 12.) The overall effects are similar to those in the unsubstituted compound: C-2,6 (-23.2), C-3,5 (-1.2) and C-4 (+2.6 ppm) in the monomethyl and C-2,6 (-22.2), C-3,5 (-0.3) and C-4 (+2.1 ppm) in the trimethylcompounds.

The γ-effect of CH_2, N and P can be compared by considering the equatorial methyl shifts in 2,5-dimethylcyclohexane, 17 and 58β.

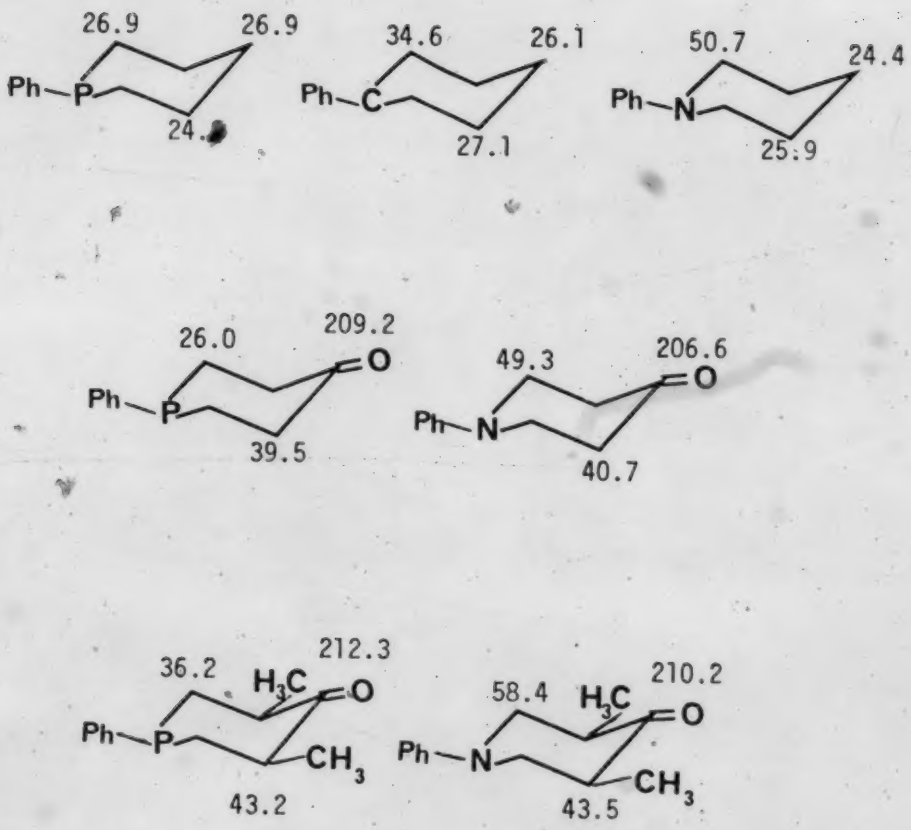
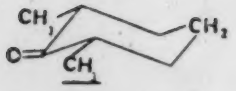


FIGURE 12: Carbon-13 chemical shifts for C-2,6, C-3,5 and C-4 carbon positions in analogous C, N and P six-membered rings.



14.6

11.4

17.5

17 (∿) 58β (∿)

Compared to cyclohexanone the nitrogen atom shields the methyl carbon while the phosphorus deshields. The former observation has already been described (Chapter II(A)) while the latter follows from the fact that third-row heteroatoms are expected to have γ-deshielding effects[34]. The phosphorus γ-effect appears to be quite general. From this study it is clear that phosphorus should be included as a γ-deshielding heteroatom for nuclei in the anti-periplaner arrangement.

D. CONCLUSIONS

This study clearly demonstrates that cmr is a valuable tool in the conformational analysis of phosphorus heterocycles. In particular, $^{2}J_{PC}$ coupling constants in phosphorinane derivatives are extremely useful in confirming conformational assignments. The phenyl orientation is assigned as equatorial in 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanol (55) rather than axial due to the observed coupling (11 Hz) to the C-3,5 carbons, It is imperative that the dihedral angle and sign of the phosphorus-carbon coupling constants in phosphorus heterocycles should be obtained so that a definite geometric relationship of the $^{2}J_{PC}$ coupling constant can be calculated. From our work we submit the approximation that the maximum coupling of 33 Hz occurs with the dihedral angle of 0° with a steady decrease in coupling to 11 Hz at

60° and 0 Hz at 180°. Distant dependent coupling was observed in the phosphorinane and phosphorinane oxides with the exception that in the latter the $^{3}J_{PC}$ coupling constants were larger than the $^{2}J_{PC}$ coupling constants. A steric-effect on $^{1}J_{PC}$ was observed with the coupling being larger to C-q when the phenyl groups was equatorial in the phosphorinanes and when the phenyl group was axial in the phosphorinane oxides.

The chair conformation of the phosphorinanes was preferred with the phenyl substituent predominately axial, with the exception of 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanol (55) in which two severe 1,3-diaxial interactions cause the chair to interconvert to the conformer with an equatorial phenyl group. The conformational changes in the molecules investigated were better followed by the $^{2}J_{PC}$ coupling constant than ^{13}C chemical shifts. The conformation of the phosphorinane oxides were found similar to the phosphorinanes, in contrast with the sulphide derivative of 1-phenylphosphorinane which are reported[73a] to undergo chair interconversion upon sulphurization. Additivity effects of sulphur and oxygen in the corresponding derivatives of 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanone (54) are similar with the exception that the β-effect of sulphur on C-2,6 is larger than that of oxygen.

The fact that no significant electron delocalization occurs from the phosphorus to the aromatic rings in arylphosphines was confirmed by the cmr study on mono-, di- and triphenylphosphine, while the electron withdrawing effect of the phosphorus-oxygen bond in the phosphine oxides of these molecules was clearly observed with the phosphorus-oxygen bond being significantly polarized ($P^{\oplus} - O^{\ominus}$).

E. EXPERIMENTAL

A sample of triphenylphosphine was obtained from Aldrich Chemical Company and used without further purification. A sample of 1-methoxy-1-oxo-4-phosphorinanone was donated by Dr. M. J. Gallagher. The compounds that were prepared by well-known methods along with the observed physical constants are given below. In all cases the boiling points and melting points are uncorrected.

Compound	Observed bp/mm or mp	Reported bp/mm or mp	Ref.
2,2,6,6-tetramethyl-1-phenyl-4-phosphorinanone	90°	91-92°	127
2,2,6,6-tetramethyl-1-phenyl-1-oxo-4-phosphorinanone	209-210°	212-213°	127
2,2,6,6-tetramethyl-4-phenyl-1-sulfide-4-phosphorinanone	135-138°	138°	127
2,2,6,6-tetramethyl-1-phenyl-4-phosphorinanol	122-124°	123-124°	127
1-phenyl-4-phosphorinanone	184-190°/1mm	185-190°/1mm	128
1-phenyl-1-oxo-4-phosphorinanone	164-166°	166°	129
1-phenylphosphorinane	192-194°/3mm	140°/1mm	130
1-phenyl-1-oxophosphorinane	126-128°	130°	131
8-phenyl-9-phosphabicyclo|3.2.1.|octan-3-one	143-145°	144-146°	126
8-phenyl-8-methyl-8-phosphonium-bicyclo|3.2.1.|-octan-3-one iodide	238-240°	239-240°	126
phenylphosphine	154-157°/730mm	155°/760mm	132
phenylphosphine oxide	81-82°	80-83°	133
diphenylphosphine	122-125°/1mm	150-154°/11mm	134
diphenylphosphine oxide	53-55°	53-55°	135
triphenylphosphine oxide	153-155°	154-155°	136

Compound	Observed bp/mm or mp	Reported bp/mm or mp	Ref.
N-phenylpiperidine	115°/10mm	110-118°/9mm	137

Synthesis of Phosphorinane and Arylphosphine Oxides

Following a reported procedure[126] the phosphorinane or arylphosphine was dissolved in acetone (pH ≈ 8) and an excess of 30% H_2O_2 was added, dropwise to the cooled solution. The mixture was stirred for 2 hrs., diluted with more acetone and washed several times with 5% $FeSO_4$ solution, then with water and then dried ($MgSO_4$). Evaporation left the oxide product which can be purified by recrystallization from ether.

2,2,6,6-Tetramethyl-1-phenylphosphorinane

A mixture of 3.85 g of the tetramethyl-4-phosphorinanone[127], 3 g of sodium hydroxide, 3.5 g of 85% aqueous hydrazine and 50 mls of diethylene glycol was refluxed at 195° for 3 hrs. It was allowed to cool, neutralized with concentrated hydrochloric acid, extracted with benzene and freeze dried. A yield of 1 g (55%) of the title compound was obtained. B.p. 60-63°.

Pmr ($CDCl_3$) CH_3(ax.)1.2$_8$ ppm J_{PH}:19 Hz, CH_3(eq) 0.8$_1$ ppm, J_{PH} 10 Hz, CH_2's 1.7 ppm (multiplet). Phenyl 7.6 - 7.9 ppm multiplet.

Characterized by formation of the oxide derivative.

2,2,6,6-Tetramethyl-1-phenyl-1-oxo-phosphorinane

Procedure as given above yielded a hydroscopic white solid of mp 60°.

Pmr ($CDCl_3$) CH_3(ax.)1.30 ppm J_{PH}:12.5 Hz, CH_3(eq) 1.0$_1$ ppm J_{PH} 14 Hz, CH_2's 1.5-2.0 ppm (multiplet) phenyl, o 7.7-8.0 ppm (multiplet), m and

p 7.4-7.6 ppm (multiplet).

I.R. (Nujol) P=O (st):1130 cm^{-1}, P-Ph (st):1460 cm^{-1}.

Mass Spec. Exact Mass. 250.1478 (measured) 250.1483 (calculated.)

Correct for $C_{15}H_{23}OP$.

2,2,6,6-Tetramethyl-1-phenyl-1-oxo-4-Phosphorinanol

Procedure as given above yielded a white solid, mp 197-200 .

Pmr ($CDCl_3$) CH_3(ax.)1.50 ppm, J_{PH} 12 Hz, CH_3(eq) 1.1$_2$ ppm, J_{PH} 12 Hz, CH and CH_2 1.7-2.4 ppm (multiplet). Phenyl o, 7.7-8.0 ppm (multiplet), m and p 7.4 - 7.6 ppm (multiplet).

I.R. Nujol) 3320 cm^{-1} (OH str), 1440 cm^{-1} (P-Ph str), 1140 cm^{-1} P=O (str).

Mass.Spec. Exact Mass. 266.1432 (measured), 266.1436 (calculated).

Correct for $C_{15}H_{23}O_2P$.

1-Phenyl-3,5-Dimethyl-4-Phosphorinanone

A mixture of 5 g of 2,4-dimethyl-3-pentadienone[89] and 5 g of phenylphosphine was heated under a nitrogen atmosphere at 60° for 3 hrs. The product was a heavy oil that could only be distilled at high temperature, bp 140°/0.2mm, lit. 103°/0.01mm. The product was subjected to column chromatography on alumina eluting with chloroform, the column being kept under a nitrogen atmosphere. The first fraction collected was a mixture of 3 isomers (cmr data given in Table XX). Further chromatography of this fraction using benzene as elutant separated one of the isomers since the major fraction collected was only a mixture of two isomers (two spots on t.l.c.). Further chromatography did not resolve these isomers.

Pmr ($CDCl_3$) of the three isomers:

CH_3 0.9_8 ppm, J_{CH} 6.4 Hz (58β), CH_3 1.0_8 ppm J_{CH} 6.5 Hz (58α), CH_3 1.2_4 ppm(s) 58γ (other methyl resonances observed). CH_2's 1.7 - 2.1 ppm (multiplet) CH's 2.2 - 2.6 ppm (multiplet) Phenyl 7.1 - 7.4 ppm (multiplet).

1-Phenyl-1-oxo-3,5-dimethyl-4-phosphorinone

A mixture of the isomers, 58α and 58β, with the former isomer dominating was subjected to oxidation as outlined earlier. A white solid of mp 122-125° was isolated which was shown by t.l.c. to be a single component. Mp (lit[120]) 124-126°.

I.R. (Nujol) 1720 cm^{-1} (C=O str), 1160 cm^{-1} P=O (str) and 1440 cm^{-1} P-PH (str).

Mass spec. m/e 236.

8-Phenyl-8-oxo-8-phosphabicyclo[3.2.1.]octan-3-one.

A 1.1g mixture of the two isomers of 8-Phenyl-8-phosphabicyclo[3.2.1.]octan-3-one was subjected to oxidation as outlined earlier using 0.61 g of 30% H_2O_2. The resulting crystalline solid after recrystallization from acetonitrile yielded 1 g of the title compound, m.p. 200-203°, however, two isomers were present as indicated by t.l.c. These isomers could not be separated using column chromatography.

I.R. (Nujol) 1750 cm^{-1} (C=O str), 1450 cm^{-1}, P-Ph (str) 1125 cm^{-1} P=O (str).

Mass spectrum m/e 234.

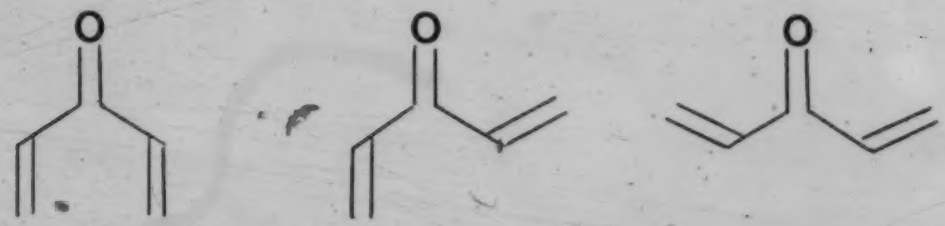
CHAPTER V

DIENONES

A. INTRODUCTION

Dienones are a particular example of cross-conjugated systems. We define cross-conjugation, following Phelan and Orchin[138], as a compound possessing three unsaturated groups, two of which although conjugated to a third unsaturated center are not conjugated to each other. The review article by Phelan and Orchin primarily concerns a molecular orbital approach to the electronic distribution and extent of conjugation between the nonconjugated centers in cross-conjugated systems, however, little reference is made to dienones. There is also a paucity of spectroscopic information on dienones. In particular only a few cholest-1,4-dien-3-one derivatives[139], phorone[83] and piperitenone[83] have been studied using carbon-13 nmr methods. Carbon-13 is ideally suited to a study of such molecules since both the extent of electron distribution and conjugation can be studied using this technique.

In the acyclic dienone system there are three possible planar conformations. However alkyl substitution at any of the olefinic



a: s-trans/s-trans b: s-trans/s-cis c: s-cis/s-cis

carbons is expected to have a dramatic effect on the dienone conformation so presenting the dienone system with two opposing forces: conjugative and steric. In all cyclic dienone systems the propensity for the dominance of conjugative forces is greater due to the imposed planarity of the ring.

Synthetic interest in dienones has been generated due to their ability to undergo condensation with primary amines (Chapter II) and primary phosphines (Chapter IV) to form nitrogen and phosphorus heterocyclic compounds, respectively. This method has been used greatly in the present work. A synthetic route to cyclopentenones via an acid-catalyzed cyclization of dienones has also recently been reported[140]. A better knowledge of the electronic distribution and extent of conjugation present in dienones is considered necessary.

A basic unit of any dienone is the α,β-unsaturated carbonyl system. The ^{13}C chemical shifts of the olefinic and carbonyl carbon nuclei of various α,β-unsaturated carbonyl compounds have been reported[83]. The variation of the olefinic shielding with alkyl substitution parallels that observed in olefinic hydrocarbons[141]. However, only two dienones, phorone and piperitenone have been examined using cmr and the olefinic and carbonyl carbon chemical shifts reported[83]. It was suggested by Marr and Stothers[83] that the high field shift of the carbonyl carbon in these dienones, compared to other α,β-unsaturated compounds was due to the additional electron density at the carbonyl carbon induced by the second double bond. In view of this statement and the conformational problem the dienones present we have determined the carbon-13 chemical shifts of a series of dienones, both acyclic and alicyclic, in order to define some general features of the dienone

cross-conjugated system.

B. RESULTS

The carbon-13 chemical shifts for the acyclic dienones and enones studied are given in Table XXIII. Results for the alicyclic rigid dienones and supporting structures are given in Table XXIV. Assignments were made using conventional techniques. Ambiguities in assignment remain for the methyl resonances in compounds 65, 69 and 70. In compound 69, C-2 is distinguished from C-4 by the typical β-deshielding effect[83] induced by the C-1' methyls at the C-2 position. The carbon-13 shifts in 66, 72 and 78 were taken from the literature[83,97,105b]. Distinction between C-1 and C-5 in 67 was made by comparing the former chemical shift with that of the analogous position in the enone, 66. The chemical shifts of 76 were re-determined and compare favourably with the literature values[142]. The methylene carbons in 73, 77 and 79 were identified by use of the endocyclic homoallylic-effect[143]. Distinction between the α and β-olefinic carbons in 81 was made using a proton-selective decoupling experiment.

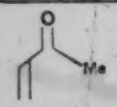
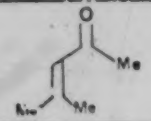
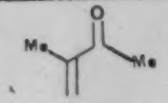
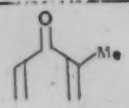
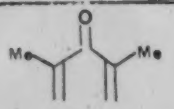
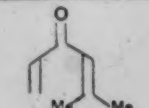
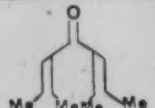
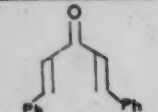
C. DISCUSSION

1. Olefinic and Carbonyl Carbons

From the carbon chemical shifts of the α- and β-olefinic carbons in both the symmetrical acyclic, 68, 70 and 71, and rigid alicyclic 74 and 81 dienones, it can be stated that there exists a contribution from the resonance forms d and f to the dienone structure. That is, the β-olefinic carbon is to low field in all cases. In

TABLE XXIII

Carbon-13 Chemical Shifts[a] of Some Acyclic Enones and Dienones

Carbon Position	64 	65 	66 	67 	68 	69 	70 	71 
C-1	26.2_7	27.4_6	b	125.1_6	124.5_7	(20.8_8)	(20.4_4)	143.1_2
C-2	198.0_9	197.9_3	198.8	145.0_1	144.5_8	156.5_0	153.8_6	125.4_8
C-3	137.7_1	124.3_5	144.3	192.2_1	199.3_9	122.3_0	126.2_9	188.6_5
C-4	128.5_0	154.5_0	125.1	131.7_9	144.5_8	189.8_4	191.1_3	125.4_8
C-5		(20.5_0)[c]		128.5_0	124.5_7	138.5_5	126.2_9	143.1_2
C-6						126.6_6	153.8_6	
C-7							(20.4_4)	
C-2'		(31.5_0)		17.7_5	18.5_0	(27.3_7)	(27.6_2)	
C-3'			b					
C-4'					18.5_0			
C-6'							(27.6_2)	

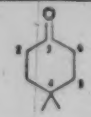
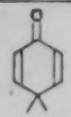
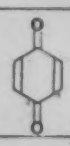
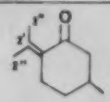
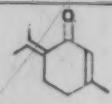
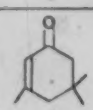
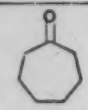
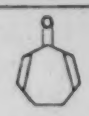
[a] Solvent $CDCl_3$ except 66 CS_2. Original data converted using $\delta_C^{CS_2} = 192.8$.

[b] Reference 83, methyl resonances not reported. Solvent effect accounted for by comparison of shifts 64, 65 and 66. Neat verses $CDCl_3$.

[c] Parenthesis indicate some uncertainty in assignment.

TABLE XXIV

Carbon-13 Chemical Shifts[a] of Alicyclic Enones, Dienones and Supporting Derivatives

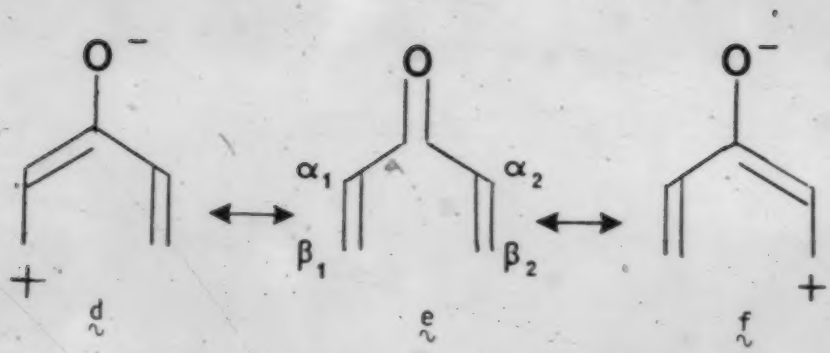
	Structure									
	72[b,c]	73	74	75	76	77	78[b]	79	80	81
Carbon Position										
C-1	209.4	198.4_1	185.0_9	187.1_9	203.7_0	191.1_3	210.5	198.6_8	214.6_5	192.4_3
C-2	38.0	126.8_3	127.2_1	136.5_9	131.8_4	128.9_3	49.0	125.3_7	43.8_0	133.5_2
C-3	39.5	159.2_5	156.5_5	136.5_9	28.5_9	28.0_0	29.5	159.6_3	(30.4_2)[d]	144.0_4
C-4	30.2	32.7_4	37.8_2	187.1_9	32.8_5	31.8_3	47.2	50.7_6	(24.3_3)	27.3_0
C-5	39.5	36.2_0	156.5_5	136.5_9	31.5_6	159.4_1	35.1	33.3_9	(24.3_3)	27.3_0
C-6	38.0	34.3_6	127.2_1	136.5_9	50.8_1	128.9_3	53.9	45.0_4	(30.4_2)	144.0_4
C-2'					141.7_7	142.1_0				
C-2"					(22.9_0)	(22.5_0)				
					(22.1_1)	(22.8_2)				
C-3'							22.4	24.3_2		
C-4'	27.8	27.6_7	26.6_0							
C-5'							25.7 32.0	28.2_1		
					21.7_4	23.7_4				
C-7									43.8_0	133.5_2

[a] Given in ppm downfield from TMS. Solvent $CDCl_3$ except 72 CS_2, original data converted using $\delta_C^{CS_2} = 192.8$ ppm.

[b] Taken from the literature: 72 reference 105b, 78 reference 97.

[c] Numbering system is shown in 72, increasing in an anti-clockwise direction.

[d] Parenthesis indicate some uncertainty in assignment.

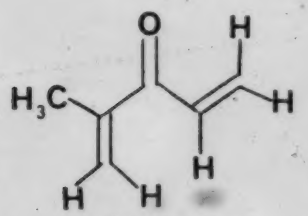


d e f

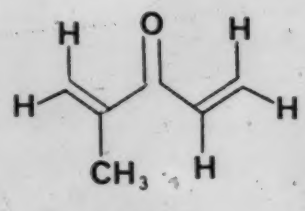
general the carbonyl group is shielded on introduction of a second double bond to the enone. A greater conjugative effect is experienced by the carbonyl group in the dienone and where the conjugative ability is further extended, as in the phenyl compound 71, the shielding is greatest (188.6_5 ppm) in the acyclic systems.

The conformation of the dienone is important when considering the additivity effects of the second double bond. In the acyclic systems, comparison of 66 and 67 give the double bond substitution parameters at the carbonyl, α- and β-olefinic carbons, -6.6, +0.7 and 0.0 ppm, respectively. While a similar comparison between 65 and 69 gives the values, -8.1, -2.0 and +2.0 ppm, respectively. Since any effects on the carbonyl and β-olefinic carbons are due to conjugative interactions the larger shielding (-8.1 ppm) at the carbonyl carbon and deshielding (+2.0 ppm) at the β-olefinic carbon in 69 than 67 (-6.6 and 0.0 ppm, respectively) is indicative of a greater extent of conjugation in the former. Mesityl oxide 65 is known to exist in the s-cis conformation[83]. Thus the dienone is conversely assumed to exist in the linear c formation. The c and b conformations of 67 have interactions between the methyl or C-1 olefinic proton with the C-4 olefinic proton, respectively. These interactions will likely cause a rotation of one of the double bonds out of the

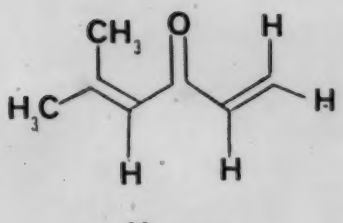
conjugative plane, hence lowering the conjugative effect at the carbonyl and β-olefinic carbons.



67:b



67:c



69:c

The cyclic dienones impart rigidity in the molecule and this appears to assist conjugation. Introduction of the double bond in 72 causes a carbonyl shielding of -11.0 ppm, similar to the effect observed in 2-cyclohexenone (-11.7 ppm)[83] and isophorone 79 (-11.8 ppm). The dienone 74 exhibits a carbonyl chemical shift of 185.0_9 ppm, at higher field than even p-benzoquinone 75 (187.1_9 ppm). This suggests that 74 is relatively planar. The shielding effect of -13.3 ppm is the largest observed in the dienone series. An x-ray study[144] of the similar compound, spirodienone, where the C-4' methyls of 74 are part of a cyclohexanone ring provides evidence for a planar conformation. Introduction of the second double bond causes the α- and β-olefinic carbons of the enone to be deshielded (+0.4 ppm) and shielded (-2.7 ppm), respectively. The latter effect is dominated by an endocyclic homoallyl shielding effect. Comparing the shifts in pulegone 76 and pipertenone 77 indicates that the carbonyl group is shielded (-12.6 ppm) while the α- and β-olefinic carbons are deshielded (+2.9 ppm) and shielded (-0.3 ppm), respectively. Again the large carbonyl shielding is indicative of a large increase in conjugation in 77 as a consequence of its planar configuration. Pulegone is considered to be

a chair structure undergoing chair-chair interconversion. From Dreiding models, pipertenone appears to be almost planar with C-3 projecting slightly out of the plane of the ring.

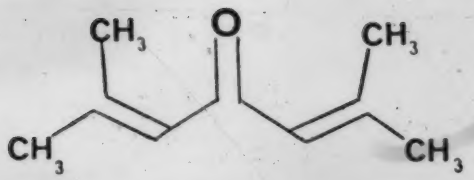
Cycloheptadienone 81 is an extremely rigid molecule, the double bonds causing the carbonyl of cycloheptanone (214.6_5 ppm) to be shielded (-22.2 ppm) which compares to the similar shift difference in 72 (-23.7 ppm) indicating the dienone part of the ring in 81 is planar.

2. Methyl Carbons

The methyl groups in 65, 69 and 70 can be assigned with the methyl cis to the carbonyl group being to low field. Comparison of 65 and 69 shows that one of the methyl resonances is deshielded by 4.1 ppm. It is expected that the anisotropic effect of the carbonyl group may be different in the dienone so causing greater deshielding of the cis methyl since the conformations of both 65 and 69 are s-cis.

The effect of methyl substitution at the α-olefinic carbon on the dienone 67 results in deshielding of the carbonyl carbon (+7.2 ppm) while similar substitution in the enone 64 causes only a 0.7 ppm deshielding effect. This difference is due to a conformational change in 67 to 68. The dienone 68 is considered to be a non-planar molecule since severe 1,5-steric interactions occur in the planar conformation. Thus the carbonyl deshielding in 68 is taken to represent a decrease in conjugation rather than an α-methyl substituent effect.

The conformation of 70 is expected to be similar to the planar c conformation of 69 since the methyl resonances are identical in both dienones. Hence the two β-methyl substituent effects can be obtained, carbonyl (-1.3 ppm), α-olefin (-12.4 ppm) β-olefin (+27.3 ppm).



70:c
~ ~

These values compare favourably with those between the enones 64 and 65, -0.2, -13.4 and +26.0 ppm, respectively. The 1 ppm difference in these parameters may arise from conformational differences since the conformation of 64 is not known.

On examining Drieding models the equivalence of the C-4' methyls in 73 suggest the molecule exists in a half-chair conformation in equilibrium:

The C-5' methyls are also equivalent (28.2_1 ppm) in 79 supporting the half-chair conformational equilibrium in this molecule.

D. CONCLUSIONS

The substitution effect of the second double bond on the carbonyl carbon in the acyclic dienone series has a lower shielding effect (-8.1 ppm) than found upon formation of the enone (-9.4 ppm, calculated from acetone 207.5 ppm[85], methyl vinyl ketone 64 (198.1 ppm).

As in the enones, co-planarity of the components of the conjugated system in the dienones is the most important factor governing the position of the carbonyl chemical shift. Therefore, additivity parameters for substitution at the α- and β-olefinic carbons must take into account changes from co-planarity due to steric effects. A greater extent of conjugation exists in the alicyclic dienones, the dienone ring being relatively planar in the molecules studied. The second double bond substitution effect in these dienones shields the carbonyl carbon to a greater extent (-13.3 ppm) than the introduction of the first double bond (-11.0 ppm) in the enones.

This study shows that the ^{13}C spectrum provides diagnostic evidence for the identification and degree of co-planarity in the dienone cross-conjugated system. The statement of Marr and Stothers[83] (page 139) can be extended to cover dienones both acyclic and alicyclic with the dienone structure consisting of a contribution of the resonance forms which have conjugation between non-conjugated centers in the cross-conjugated system.

E. EXPERIMENTAL

Some of the compounds studied are commercially available and were obtained from the following sources and were used without further purification. Aldrich Chemical Co., Inc., methyl vinyl ketone, mesityl oxide, butenone, phorone, p-benzoquinone, pulegone and cycloheptanone. Eastman Organic Chemicals, 1,5-diphenyl-3-pentadienone. A sample each of 4,4-dimethyl-2-cyclohexenone and isophorone was donated by Mr. E. Browne and Dr. P. Georghiou, respectively. The remaining compounds were prepared by well-known methods. The observed

physical constants and the synthesis employed are given below. In these cases the boiling points and melting points are uncorrected.

Compound	Observed b.p./mm.	Reported b.p./mm.	Reference
4,4-Dimethyl-2,5-cyclohexadienone	77-79/10	41/0.15	145
Piperitenone	120-125/10	125/10	146
2,6-Cycloheptadienone	65-66/2	50.5-51/1	147
2-Methyl-1,4-pentadien-3-one	62-65/100	59/95	148
2-Methyl-2,5-hexadien-4-one	60-65/20	60/22	148
2,4-Dimethyl-1,4-pentadien-3-one	75-78/100	72/110	89

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